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(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033–0530 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DUGAR, Sundeep [IN/US]; 749 Wingate Drive, Bridgewater, NJ 08807 (US). NEUSTADT, Bernard, R. [US/US]; 24 Brook Place, West Orange, NJ 07052 (US). STAMFORD, Andrew, W. [US/US]; 27 Overlook Road, Chatham Township, NJ 07928 (US). WU, Yusheng [CN/US]; Apartment 20C, 235 East 40th Street, New York, NY 10016 (US).

(74) Agents: MAGATTI, Anita, W. et al.; Schering–Plough Corporation, Patent Dept. K–6–1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033–0530 (US).

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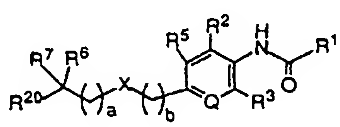

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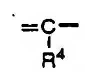

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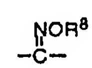

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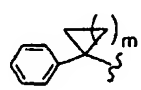

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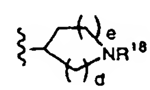

(iv)

(57) Abstract

Compounds of formula (I) or a pharmaceutically acceptable salt thereof, wherein a and b are 0–2, provided that the sum is 0–3; Q is (i) or (–N=); X is –O–, –S–, –SO–, $-SO_2-$, $-CH(OR^8)-$, –C(O)–, $-C(R^{23})_2-$, optionally substituted alkenyl, alkynyl or (ii); R^1 is optionally substituted aryl, heteroaryl, substituted amino, alkyl–$OC(O)R^8$, aryloxyalkyl, (iii) wherein m is 1–4, or (iv) wherein d and e are 0–2; R^2, R^3, R^4 and R^5 are H, alkyl, optionally substituted cycloalkyl, halogen, $-OR^8$, $-N(R^8)_2$, $-CO_2R^8$ or CF_3; R^6 and R^7 are H, alkyl, alkenyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, cycloalkyl or cycloalkylalkyl, or R^6 and R^7, form a 3–7–membered carbocyclic ring, or a 4–7–membered heterocyclic ring; R^8 is H, alkyl, cycloalkyl, optionally substituted aryl or heteroaryl; R^9 is alkyl, cycloalkyl, optionally substituted aryl or heteroaryl; R^{11} is H, alkyl or cycloalkyl; and R^{23} is R^8 or halogen; are claimed, as well as additional novel compounds; also claimed are pharmaceutical compositions and methods of using said novel compounds in the treatment of eating disorders and diabetes.

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NEUROPEPTIDE Y5 RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

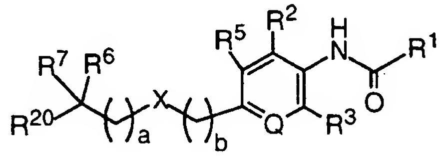
The present invention relates to selective neuropeptide Y Y5 receptor antagonists useful in the treatment of eating disorders and diabetes, pharmaceutical compositions containing the compounds, and methods of treatment using the compounds.

Neuropeptide Y is a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems. This peptide mediates a number of physiological effects through its various receptor subtypes. Studies in animals have shown that neuropeptide Y is a powerful stimulus of food intake, and it has been demonstrated that activation of neuropeptide Y Y5 receptors results in hyperphagia and decreased thermogenesis. Therefore compounds that antagonize neuropeptide Y at the Y5 receptor subtype represent an approach to the treatment of eating disorders such as obesity and hyperphagia.

Phenyl amides and ureas are known as antiatherosclerotic agents, see for example U.S. 4,623,662, and benzoic acid amides are disclosed as antidiabetic agents in U.S. 5,378,728. N,N-alkylenebis-(benzamides) are known as endocrinological agents, see U.S. 4,009,208. WO 98/35957, published August 20, 1998, discloses amide derivatives as selective neuropeptide Y receptor antagonists.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by the structural formula I



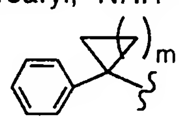
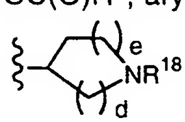
I

or a pharmaceutically acceptable salt thereof, wherein

a and b are independently 0, 1 or 2, provided that the sum of a and b is 0 to 3;

Q is $=\underset{R^4}{\underset{|}{C}}-$ or $-N=$;

X is -O-, -S-, -SO-, -SO_2-, -CH(OR^8)-, -C(O)-, -C(R^{23})$_2$-, -C(R^{25})=C(R^{25})-, $-C\equiv C-$ or $-\overset{NOR^8}{\overset{\|}{C}}-$;

R^1 is R^{15}-aryl, R^{24}-heteroaryl, -NHR^{12}, -N(R^{12})$_2$, -(C_1-C_9)alkyl-OC(O)R^8, aryloxy(C_1-C_9)alkyl,  wherein m is 1-4, or  wherein d and e are independently 0, 1 or 2;

R^2, R^3, R^4 and R^5 are independently selected from the group consisting of H, C_1-C_5 straight or branched alkyl, (C_3-C_{12})cycloalkyl, R^{14}-(C_3-C_{12})cycloalkyl, halogen, -OR^8, -N(R^8)$_2$, -CO_2R^8 and CF_3;

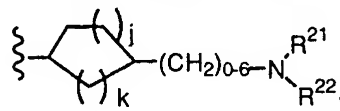
R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_9)alkyl, (C_1-C_9)alkenyl, hydroxy-(C_1-C_9)alkyl, amino-(C_1-C_9)-alkyl, (C_1-C_9)alkoxy-(C_1-C_9)alkyl, (C_3-C_{12})cycloalkyl and (C_3-C_{12})-cycloalkyl-(C_1-C_6)alkyl, or R^6 and R^7, together with the carbon to which they are attached, form a 3, 4, 5, 6 or 7-membered carbocyclic ring, or a 4, 5, 6 or 7-membered heterocyclic ring, wherein 1, 2 or 3 ring members are independently selected from the group consisting of O, S and N;

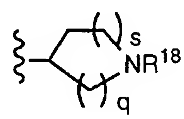
R^8 is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, R^{15}-aryl and R^{24}-heteroaryl;

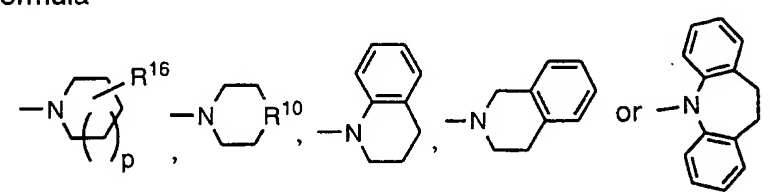
R^9 is (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, R^{15}-aryl or R^{24}-heteroaryl;

R^{11} is independently selected from the group consisting of H, (C_1-C_6)alkyl and (C_3-C_{12})cycloalkyl;

R^{12} is independently selected from the group consisting of straight or branched $(C_1\text{-}C_9)$alkyl, hydroxy$(C_2\text{-}C_9)$alkyl, $(C_1\text{-}C_9)$alkoxy-$(C_2\text{-}C_9)$-alkyl, $N(R^{11})(R^{19})$-$(C_2\text{-}C_9)$-alkyl, $HS(C_2\text{-}C_9)$-alkyl, $(C_1\text{-}C_9)$-alkylthio-$(C_2\text{-}C_9)$-alkyl, $(C_3\text{-}C_{12})$-cycloalkyl, R^{14}-$(C_3\text{-}C_{12})$ cycloalkyl, R^{15}-aryl,
R^{24}-heteroaryl, R^{15}-aryl$(C_1\text{-}C_6)$-alkyl, R^{24}-heteroaryl$(C_1\text{-}C_6)$-alkyl,


wherein j and k are independently 0, 1 or 2,

and  wherein q is 1 or 2, and s is 0, 1 or 2; or two R^{12} groups, together with the nitrogen to which they are attached, form a ring of the formula



wherein p is 0, 1 or 2;

R^{10} is $-NR^{18}$-, -O- or -S-;

R^{13} is 1 to 3 substituents independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, halogen, $(C_1\text{-}C_6)$alkoxy and CF_3;

R^{14} is 1 to 3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, benzyl, R^{13}-aryl and R^{13}-heteroaryl;

R^{15} is 1 to 3 substituents independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, halo, polyhalo$(C_1\text{-}C_6)$alkyl, $R^{17}O$-, $-N(R^{17})_2$, $-S(R^{17})$, $R^{17}O$-$(C_1\text{-}C_6)$alkyl, $(R^{17})_2N$-$(C_1\text{-}C_6)$alkyl, formyl, $-C(O)R^{17}$, $-COOR^{17}$, $-CON(R^{17})_2$, $-OC(O)N(R^{17})_2$, $-N(R^{17})C(O)N(R^{17})_2$, $-NR^{17}C(O)R^{17}$, $-NR^{17}C(O)OR^{14}$, $R^{17}S(O)$-, $R^{17}SO_2$-, $R^{17}SO_2NR^{17}$- and tri$(C_1\text{-}C_6)$-alkylsilyl;

R^{16} is 1-3 substituents independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{12})$spirocyclo-alkyl, $(C_3\text{-}C_4)$spiro-alkylenedioxy, R^{15}-aryl, R^{24}-heteroaryl, benzyl, N-piperidinyl, $-COR^8$, $-C(O)NR^8R^9$, $-NR^8R^9$ and $-NR^8C(O)R^9$, or when two R^{16} groups are attached to adjacent ring carbon atoms, together with said carbon atoms, they can form a $(C_5\text{-}C_7)$cycloalkyl ring;

R^{17} is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, (C_3-C_{12})cycloalkyl(C_1-C_6)alkyl, R^{13}-aryl and R^{13}-heteroaryl;

R^{18} is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, (C_3-C_{12})cycloalkyl-(C_1-C_6)alkyl, R^{15}-aryl, R^{24}-heteroaryl, $-CO_2R^9$, $-C(O)N(R^8)_2$, $-COR^8$ and $-SO_2R^9$;

R^{19} is H, (C_3-C_{12})cycloalkyl-(C_1-C_6)alkyl, R^{15}-aryl, R^{24}-heteroaryl, $-CO_2R^9$, $-C(O)N(R^8)_2$, $-COR^8$ or $-SO_2R^9$;

R^{20} is (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, (C_3-C_{12})cycloalkyl-(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, oxo(C_1-C_6)alkyl or polyhalo(C_1-C_6)alkyl;

R^{21} and R^{22} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl-(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, R^{15}-aryl, R^{24}-heteroaryl, R^{15}-aryl(C_1-C_6)alkyl or R^{24}-heteroaryl(C_1-C_6)-alkyl;

R^{23} is independently selected from the group consisting of H, halogen, (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, R^{15}-aryl, and R^{24}-heteroaryl;

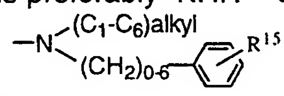
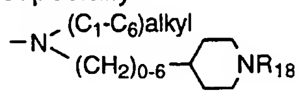
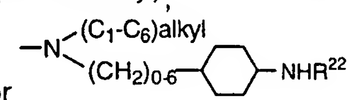
R^{24} is 1 to 2 substituents independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, halo, polyhalo(C_1-C_6)alkyl, $R^{17}O-$, $-N(R^{17})_2$, $-S(R^{17})$, $R^{17}O-(C_1-C_6)$alkyl, $(R^{17})_2N-(C_1-C_6)$alkyl, formyl, $-C(O)R^{17}$, $-COOR^{17}$, $-CON(R^{17})_2$, $-OC(O)N(R^{17})_2$, $-N(R^{17})C(O)N(R^{17})_2$, $-NR^{17}C(O)R^{17}$, $-NR^{17}C(O)OR^{14}$, $R^{17}S(O)-$, $R^{17}SO_2-$, $R^{17}SO_2NR^{17}-$ and tri(C_1-C_6)-alkylsilyl; and

R^{25} is independently selected from the group consisting of hydrogen, halogen, (C_1-C_6)-alkyl and polyhalo(C_1-C_6)alkyl.

In a preferred group of compounds of formula I , Q is $\underset{R^4}{=\overset{}{C}-}$ wherein R^4 is H. Also preferred are compounds wherein R^3 is H, and wherein R^2 and R^5 are independently H or halogen. R^6 and R^7 are preferably (C_1-C_9)alkyl, especially methyl, or R^6 and R^7, together with the carbon to which they are attached, form a C_3-C_6 carbocyclic ring.

In compounds of formula I, X is preferably -S-; -C(O)-; or $-C(R^8)_2$, especially wherein R^8 is H. More preferably, X is $-C(R^8)_2-$, and compounds wherein X is $-CH_2-$ are especially preferred.

In compounds of formula I, a is preferably 1 or 2 and b is preferably 0.

In compounds of formula I, R^1 is preferably $-NHR^{12}$ or $-N(R^{12})_2$, especially $-N<^{(C_1\text{-}C_6)alkyl}_{(CH_2)_{0\text{-}6}\text{-}(R^{24}\text{-heteroaryl})}$;  ;  ; or  wherein R^{18} is $(C_1\text{-}C_6)$alkyl or $-SO_2R^9$; R^9 is $(C_1\text{-}C_6)$alkyl or aryl; and R^{22} is $(C_1\text{-}C_6)$-alkyl or $(C_3\text{-}C_{12})$cycloalkyl$(C_1\text{-}C_6)$alkyl.

Another aspect of the invention is a pharmaceutical composition for treating eating disorders or diabetes which comprises an effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Yet another aspect of this invention is a method of treating an eating disorder or diabetes comprising administering an effective amount of a compound of formula I to a patient in need of such treatment.

Also claimed are novel compounds similar to those of formula I wherein b is 0, X is -O- or -S- and the substituent corresponding to R^1 is optionally substituted alkyl.

DETAILED DESCRIPTION

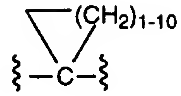
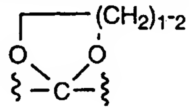
Except where stated otherwise the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "alkoxy", etc.

Alkyl represents a straight or branched saturated hydrocarbon chains having the designated number of carbon atoms. If the number of carbon atoms is not specified, e.g., if the term lower alkyl is used, chain lengths of 1 to 6 carbons are intended.

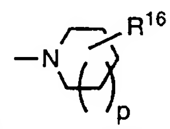
When X is $-C(R^{25})=C(R^{25})-$, both cis and trans configurations are comtemplated.

Cycloalkyl represents a saturated carbocyclic ring having 3 to 12 carbon atoms. Preferred are C_3-C_6cycloalkyl rings.

In the definition of R^{16}, the term $(C_3\text{-}C_{12})$spirocycloalkyl refers to a $(C_2\text{-}C_{11})$alkylene chain joined at both ends to the same ring carbon, i.e.,


. Similarly, the term (C_3-C_4)spiroalkylenedioxy refers to a (C_2-C_3)alkylenedioxy group joined at both ends to the same ring carbon atom, i.e.,  .

In the definition of R^6 and R^7, the term "heterocyclic ring" refers to 4- to 7-membered saturated rings comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and -NH-, with the remaining ring members being carbon. Where a heterocyclic ring comprises more than one heteroatom, no rings are formed where there are adjacent oxygen atoms, adjacent sulfur atoms, or three consecutive heteroatoms. Examples of heterocyclic rings are tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl.

When two R^{12} groups form a ring of the formula  , those skilled in the art will recognize that $-NR^8R^9$ and $-NR^8C(O)R^9$ substituents cannot be attached to a carbon adjacent to the piperizinyl nitrogen.

Halogen represents fluoro, chloro, bromo or iodo.

Polyhalo(C_1-C_6)alkyl refers to a straight or branched alkyl chain substituted by 1 to 5 halogen atoms, which can be attached to the same or different carbon atoms, e.g., $-CH_2F$, $-CHF_2$, $-CF_3$, F_3CCH_2- and $-CF_2CF_3$.

Hydroxy(C_1-C_6)alkyl refers to an alkyl chain substituted on any substitutable carbon by a hydroxy group. Similarly, oxo(C_1-C_6)alkyl refers to an alkyl chain substituted by an =O moiety.

Aryl represents phenyl or naphthyl.

Heteroaryl refers to 5- to 10-membered single or benzofused aromatic rings comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and -N=, provided that the rings do not include adjacent oxygen and/or sulfur atoms.. Examples of single-ring heteroaryl groups are pyridyl, isoxazolyl, oxadiazolyl, furanyl,

pyrrolyl, thienyl, imidazolyl, pyrazolyl, tetrazolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazolyl. Examples of benzofused heteroaryl groups are quinolinyl, isoquinolinyl, quinazolinyl, thianaphthenyl (i.e., benzothienyl), indolyl, benzimidazolyl, benzofuranyl and benzofurazanyl. N-oxides of nitrogen-containing heteroaryl groups are also included. All positional isomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl. Preferred heteroaryl groups are pyridyl, isoxazolyl, thienyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl and quinazolinyl.

When a variable appears more than once in the structural formula, for example R^8, the identity of each variable appearing more than once may be independently selected from the definition for that variable.

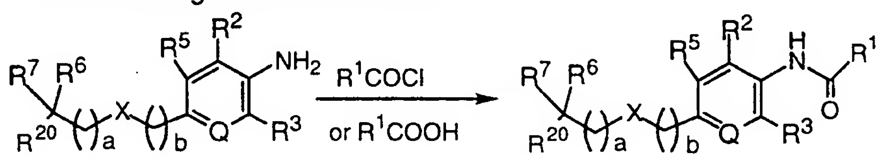
For compounds of the invention having at least one asymmetrical carbon atom, all isomers, including diastereomers, enantiomers and rotational isomers are contemplated as being part of this invention. The invention includes d and i isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of formula I.

Compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

A compound of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as

dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

Compounds of formula I may be produced by processes known to those skilled in the art as shown in the examples below. Typically, the claimed compounds wherein X is -S- or -O- can be prepared as shown in the following reaction scheme:



II IA

wherein an amine of formula II is reacted with an acid chloride or carbamoyl chloride in the presence of a base, or with a carboxylic acid in the presence of standard amide coupling agents such as EDC and DMAP. Starting materials of formula II can be prepared using known methods.

The compounds of formula I exhibit selective neuropeptide Y5 antagonizing activity, which has been correlated with pharmacological activity for treating eating disorders such as obesity and hyperphagia.

The compounds of formula I display pharmacological activity in test procedures designated to indicate neuropeptide Y5 receptor antagonist activity. The compounds are non-toxic at pharmaceutically therapeutic doses. Following are descriptions of the test procedures.

cAMP Assay

CHO cells expressing the various NPY receptor subtypes were maintained in Ham's F-12 media (Gibco-BRL) supplemented with 10% FCS (ICN), 1% penicillin-streptomycin, 1% non-essential amino acids and 200 μg/ml Geneticin® (GibcoBRL #11811-031) under a humidified 5% CO_2 atmosphere. Similarly, HEK-293 cells expressing the various NPY receptor subtypes were maintained in Dulbecco's modified Eagle's media (Gibco-BRL) supplemented with 10% FCS (ICN), 1% penicillin-streptomycin and 200 μg/ml Geneticin® (GibcoBRL #11811-031) under a humidified 5% CO_2 atmosphere. Two days prior to assay, cells were

released from T-175 tissue culture flasks using cell dissociation solution (1X; non-enzymatic [Sigma #C-5914]) and seeded into 96-well, flat-bottom tissue culture plates at a density of 15,000 to 20,000 cells per well. After approximately 48 hours, the cell monolayers were rinsed with Hank's balanced salt solution (HBSS) then preincubated with approximately 150 µl/well of assay buffer (HBSS supplemented with 4 mM $MgCl_2$, 10 mM HEPES, 0.2% BSA [HH]) containing 1 mM 3-isobutyl-1-methylxanthine ([IBMX] Sigma #I-5879) with or without the antagonist compound of interest at 37°C. After 20 minutes the 1 mM IBMX-HH assay buffer (± antagonist compound) was removed and replaced with assay buffer containing 1.5 µM (CHO cells) or 5 µM (HEK-293 cells) forskolin (Sigma #F-6886) and various concentrations of NPY in the presence or absence of one concentration of the antagonist compound of interest. At the end of 10 minutes, the media were removed and the cell monolayers treated with 75 µl ethanol. The tissue culture plates were agitated on a platform shaker for 15 minutes, after which the plates were transferred to a warm water bath in order to evaporate the ethanol. Upon bringing all wells to dryness, the cell residues were resolubilized with 250 µl FlashPlate® assay buffer. The amount of cAMP in each well was quantified using the [^{125}I]-cAMP FlashPlate® kit (NEN #SMP-001) and according to the protocol provided by the manufacturer. Data were expressed as either pmol cAMP/ml or as percent of control. All data points were determined in triplicate and EC_{50}'s (nM) were calculated using a nonlinear (sigmoidal) regression equation (GraphPad Prism™). The K_B of the antagonist compound was estimated using the following formula:

$$K_B = [B] / (1 - \{[A'] / [A]\})$$

where [A] is the EC_{50} of the agonist (NPY) in the absence of antagonist,

[A'] is the EC_{50} of the agonist (NPY) in the presence of antagonist, and

[B] is the concentration of the antagonist.

NPY Receptor Binding Assay

Human NPY receptors were expressed in CHO cells. Binding assays were performed in 50 mM HEPES, pH. 7.2, 2.5 mM $CaCl_2$, 1 mM

$MgCl_2$ and 0.1% BSA containing 5-10 ug of membrane protein and 0.1 nM ^{125}I-peptide YY (for NPY1, NPY2 and NPY5 receptors) or 0.1 nM ^{125}I-pancreatic polypeptide (NPY4 receptor) in a total volume of 200 ul. Non-specific binding was determined in the presence of 1 uM NPY. The reaction mixtures were incubated for 90 minutes at 30° C (NPY1 receptor) or at room temperature (NPY2, NPY4 and NPY5 receptors), then filtered through Millipore MAFC glass fiber filter plates which had been pre-soaked in 0.5% polyethyleneimine. The filters were washed with phosphate-buffered saline, and radioactivity was measured in a Packard TopCount scintillation counter.

For the compounds of this invention, a range of neuropeptide Y5 receptor binding activity from about 0.1 to about 1000nM was observed. Compounds of this invention preferably have a binding activity in the range of about 0.1 to 250 nM, more preferably about 0.1 to 100 nM, and most preferably about 0.1 to 10 nM.

For preparing pharmaceutical compositions from the compounds of formula I, pharmaceutically acceptable, inert carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as dilutents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parentertal administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit.

The invention also contemplates alternative delivery systems including, but not necessarily limited to, transdermal delivery. The transdermal compositions can take the form of creams, lotions and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation such as packeted tablets, capsules and powders in vials or ampules. The unit dosage form can also be a capsule, cachet or tablet itself, or it may be the appropriate number of any of these in a packaged form.

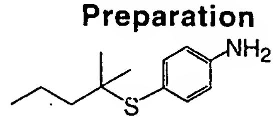
The quantity of active compound in a unit dose preparation may be varied or adjusted from about 0.5 mg to 500 mg, preferably about 0.5 to 100 mg, according to the particular application and the potency of the active ingredient and the intended treatment. The composition may, if desired, also contain other therapeutic agents.

The daily dosage is about 0.01 to about 20 mg/kg. The dosage may be varied depending on the requirement of the patient, the severity of the condition being treated and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of those in the medical art. For convenience, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

The invention disclosed herein is exemplified by the following examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

In the examples, the following abbreviations are used: phenyl (Ph), acetyl (Ac), ether (Et_2O), ethyl acetate (EtOAc), dimethylformamide (DMF) and ethanol (EtOH). Room temperature is RT.

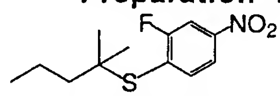
Preparation 1



1

To a stirred mixture of 4-aminothiophenol (12.52 g, 0.100 mol) and 2-methyl-1-pentene (25.30 g, 0.300 mol) in anhydrous Et_2O (100 ml) was added concentrated H_2SO_4 (15.3 ml, 0.300 mol) cautiously. The clear solution was stirred for 45 min, then poured into cold sat'd $NaHCO_3$ (200 ml). The resultant white solid was collected, washed with cold water several times and dried *in vacuo* to afford **1** (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, 2H, J = 8.7 Hz, ArH), 6.68 (d, 2H, J = 8.6 Hz, ArH), 1.47 (m, 4H, $\underline{CH_2CH_2}CH_3$), 1.24 (s, 9H, $(\underline{CH_3})_3C$), 0.97 (t, 3H, J = 7.0 Hz, $CH_2\underline{CH_3}$).

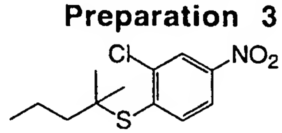
Preparation 2



2

A mixture of 3,4-difluoronitrobenzene (1.0 ml, 9.03 mmol) and $Na_2S \cdot 9H_2O$ (3.25 g, 13.5 mmol) in DMF (10 ml) was stirred at RT for 20 h, then poured into cold water. The whole was extracted with CH_2Cl_2 (3x100 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. To the residue was added 2-methyl-1-pentene (2.2 ml, 18.1 mmol) and Et_2O (5.0 ml). To the vigorously stirred mixture was slowly added concentrated H_2SO_4 (1.0 ml). After 1 h the reaction mixture was poured into cold water. The whole was extracted with CH_2Cl_2 (3x100 ml), and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash column chromatography (1:20 EtOAc/hexanes) afforded **2** (100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (m, 2H, ArH), 7.34 (t, 1H, ArH), 1.59 (m, 4H, $CH_3\underline{CH_2CH_2}$), 1.37 (s, 6H, $C(\underline{CH_3})_2S$), 1.01 (m, 3H, $\underline{CH_3}CH_2CH_2$).

Preparation 3

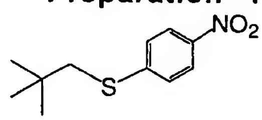


3

A mixture of S-(1,1-dimethylbutyl)thiouronium 4-toluene-sulfonate (prepared as described: Evans, M. B.et al., *J. Chem. Soc.*, (1962), p. 5045) (5.00 g, 15.0 mmol), KOH (2.10 g, 37.5 mmol) and concentrated NH_3 (1 drop) in EtOH (20 ml) was refluxed for 1 h. To the reaction mixture was added 3-chloro-4-fluoronitrobenzene in EtOH (10 ml). The mixture was refluxed for 0.5 h, allowed to cool and poured into cold water. The whole was extracted with CH_2Cl_2 (3x100 ml). The combined

organic layers were dried (Na_2SO_4), filtered and concentrated to afford **3** (84%) which was used without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (d, 1H, J=2.4 Hz, $\underline{ArH}$), 8.09 (dd, 1H, J = 2.4, 8.5 Hz, $\underline{ArH}$), 7.78 (d, 1H, J=8.5 Hz, $\underline{ArH}$), 1.62 (m, 4H, $CH_3\underline{CH_2CH_2}$), 1.40 (s, 6H, $C(\underline{CH_3})_2S$), 0.98 (m, 3H, $\underline{CH_3}CH_2CH_2$).

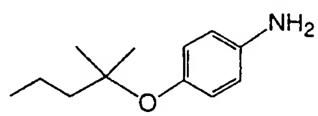
Preparation 4



4

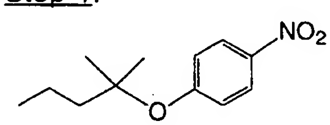
A mixture of 4-nitrothiophenol (500 mg, 3.22 mmol), 1-iodo-2,2-dimethylpropane (0.43 ml, 4.8 mmol), and NaH (80%, 97 mg, 3.2 mmol) in DMF (10 ml) was stirred for 3 days. The reaction mixture was poured into H_2O and the whole was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was subjected to flash chromatography (1:50 EtOAc/hexanes) to afford **4** (190 mg, 26%) as a solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.07 (m, 2H, $\underline{ArH}$), 7.31 (m, 2H, $\underline{ArH}$), 2.93 (s, 2H, $\underline{CH_2}S$), 1.05 (s, 9H, $(CH_3)_3$).

Preparation 5



5

Step 1:



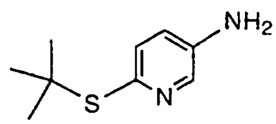
6

To an ice-cold solution of 2-methyl-2-pentanol (1.5 ml, 15 mmol) in DMF (20 ml) was added NaH (60% dispersion in mineral oil, 600 mg, 15 mmol) under a N_2 atmosphere. The cold bath was removed and the suspension was stirred for 4h. The mixture was cooled in an ice bath, 4-fluoronitrobenzene (1.1 ml, 10 mmol) was added in one portion, and the reaction mixture was stirred at RT. After 18 h, the reaction mixture was poured onto an ice-water slurry (300 ml) and extracted with Et_2O (3x200 ml). The combined Et_2O extracts were washed with H_2O (6x200 ml) and saturated NaCl, dried ($MgSO_4$), filtered and evaporated to afford an oil (2.4 g). Flash chromatography (3:1 hexanes/CH_2Cl_2) of the crude product gave **6** (1.50 g, 67%) as an oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22 (2H, m, ArH), 7.09 (2H, m, ArH), 1.77 (2H, m, $-OC(CH_3)_2\underline{CH_2}-$), 1.52

(2H, m, -<u>CH_2</u>CH_3), 1.47 (6H, s, -$OC(CH_3)_2$-), 1.03 (3H, t, $J = 7.3$ Hz, -CH_2<u>CH_3</u>). MS (CI) *m/e* 224 $(M+H)^+$.

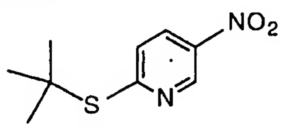
<u>Step 2</u>: A mixture of **6** (1.40 g, 6.3 mmol) and 10% Pd/C (0.14 g) in CH_3OH (40 ml) was stirred under a balloon of H_2. After 16 h, the catalyst was removed by filtration through celite, and the filter pad was washed with CH_3OH. The combined filtrate and washings were evaporated to afford **5** as an oil (1.21 g, 100%). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.83 (2H, m, ArH), 6.66 (2H, m, ArH), 1.61 - 1.50 (4H, m, -CH_2CH_2-), 1.25 (6H, s, -$OC(CH_3)_2$-), 0.98 (3H, t, $J = 7.1$ Hz, -CH_2<u>CH_3</u>).

Preparation 6



7

<u>Step 1</u>:

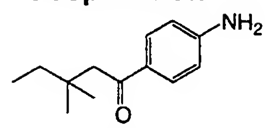


8

To a solution of 2-chloro-5-nitropyridine (1.00 g, 6.3 mmol) in EtOH (10 ml) was added a solution of potassium 2-methyl-2-propanethiolate prepared from 2-methyl-2-propanethiol (0.71ml, 6.3 mmol) and KOH (0.56 g, 10 mmol) in EtOH (10 ml). The reaction mixture was refluxed for 0.25 h, then cooled in ice. The solid was removed by filtration through celite and the filtrate was evaporated to a syrup, which was dissolved in CH_2Cl_2 (100 ml) and washed with sat'd NH_4Cl. The organic layer was dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by flash chromatography (1:4 CH_2Cl_2/hexanes) gave **8** (0.80 g, 60%) as a waxy solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.31 (1H, d, $J = 2.8$ Hz, ArH), 8.23 (1H, dd, $J = 8.9, 2.8$ Hz, ArH), 7.28 (1H, d,$J = 8.9$ Hz, ArH), 1.70 (9H, s, -$S(CH_3)_3$).

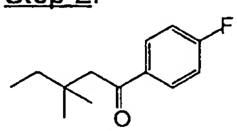
<u>Step 2</u>: To a solution of **8** (414 mg, 1.95 mmol) and $NiCl_2.6H_2O$ (950 mg, 4.0 mmol) in CH_3OH (20 ml) was added $NaBH_4$ (301 mg, 8.0 mmol) in small portions. After 20 min. the reaction mixture was concentrated and the residue was purified by flash chromatography (3:97 CH_3OH/CH_2Cl_2) to give **7** (120 mg, 34%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (1H, d, $J = 2.4$ Hz, ArH), 7.43 (1H, d, $J = 8.3$ Hz, ArH), 7.30 (1H, dd,$J = 8.3, 2.4$ Hz, ArH), 6.9 (2H, bs, NH_2), 1.43 (9H, s, -$S(CH_3)_3$).

Preparation 7



Step 1: A mixture of 3,3-dimethylpentanoic acid (11.00 g, 84.0 mmol; Synthesis (1985), 493) and $SOCl_2$ (80.0 g, 678 mmol) was refluxed for 2 h. The reaction mixture was concentrated *in vacuo* to afford the acid chloride as a colorless oil (10.0 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.83 (2H, s, $\underline{CH_2}CO$), 1.39 (2H, q, J = 7.3 Hz, $CH_3\underline{CH_2}$), 1.02 (6H, s, $C\underline{(CH_3)_2}$), 0.86 (3H, t, J = 7.3 Hz, $\underline{CH_3}CH_2$).

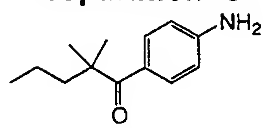
Step 2:



To an ice-cold solution of the product of Step 1 (6.00 g, 41.0 mmol) in dry Et_2O (40 ml) was slowly added 1.0 M 4-fluorophenylmagnesium bromide in THF (37 ml, 37 mmol). The reaction mixture was stirred at 0 °C for 3 h, then poured into 1N HCl solution (100 ml). The whole was extracted with EtOAc (3x100 ml) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography (hexane) afforded the product (7.00 g, 82%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (2H, m, ArH), 7.05 (2H, m, ArH), 2.80 (2H, s, $\underline{CH_2}CO$), 1.4 (2H, q, J = 8.0 Hz, $CH_3\underline{CH_2}$), 0.87 (6H, s, $\underline{(CH_3)_2C}$), 0.85 (3H, t, J = 7.6 Hz, $CH_3\underline{CH_2}$). MS (ES) *m/e* 209 $(M+H)^+$.

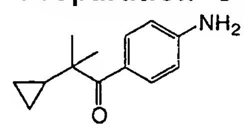
Step 3: To a solution of the product of Step 2 (2.00 g, 9.60 mmol) in DMSO (20.0 ml) in a sealed tube was added NaN_3 (6.24 g, 96.0 mmol). The vigorously stirred reaction mixture was heated at 140 °C for 5 days, then allowed to cool to RT and poured into 1N NaOH (100 ml). The whole was extracted with EtOAc (3x100 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (1:4 EtOAc/hexane) afforded Preparation 7 (0.66g, 33%) as a light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (2H, d, J = 8.8 Hz, ArH), 6.70 (2H, d, J = 8.8 Hz, ArH), 2.74 (2H, s, $\underline{CH_2}CO$), 1.40 (2H, q, J = 7.6 Hz, $\underline{CH_2}CH_3$), 0.98 (6H, s, $\underline{(CH_3)_2C}$), 0.86 (3H, t, J = 7.6 Hz, $\underline{CH_3}CH_2$). MS (FAB) *m/e* 206 $(M+H)^+$.

Preparation 8

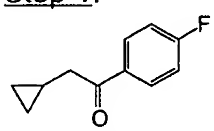


Using 2,2-dimethylpentanoic acid as the starting material and the three-step procedure described for Preparation 7, the title compound was prepared: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (2H, m), 6.61 (2H, m), 4.05 (2H, bs), 1.76 (2H, m), 1.30 (6H, s), 1.20 (4H, m), 0.83 (3H, t, J = 7.8 Hz). MS *m/e* 206 $(M+H)^+$.

Preparation 9

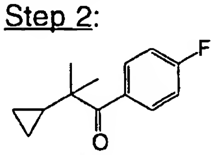


Step 1:



To an ice-cold solution of cyclopropylacetonitrile (4.7 g, 58 mmol) in anhydrous Et_2O (30ml) was added 2M 4-fluorophenylmagnesium bromide in Et_2O (25 ml, 50 mmol), and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to RT and stirred for an additional 2 h. The pH was adjusted to 3 by addition of 1N HCl and the whole was extracted with Et_2O (4x50 ml). The combined Et_2O layers were washed with saturated Na_2CO_3 and NaCl, dried ($MgSO_4$), filtered and concentrated. Flash chromatography (2:98 EtOAc/hexane) of the residue afforded the product (5.02g, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98(2H, m), 7.13 (2H, t), 2.85 (2H, d), 1.15 (1H, m), 0.61 (2H, m), 0.19 (2H, m). MS *m/e* 179 $(M+H)^+$.

Step 2:

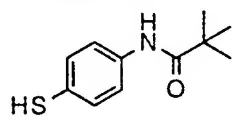


To a stirred, ice-cold solution of the product of Step 1 (5.0 g, 28 mmol) in anhydrous THF (100 ml) under N_2 was added KH (16.0 g, 35% in mineral oil, 140 mmol), and the reaction mixture was stirred for 0.5 h. Then CH_3I (16 ml, 280 mmol) was added dropwise to the ice-cold reaction mixture. After stirring at RT for 4h, the reaction mixture was

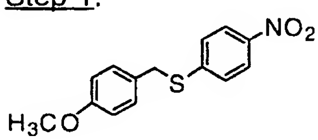
cooled in an ice-bath and sat'd NH_4Cl was cautiously added. The whole was extracted with EtOAc (3x100 ml), washed with H_2O and sat'd NaCl, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexanes, then 1:9 EtOAc/hexanes) afforded the product (3.96 g, 68%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (2H, m), 7.07 (2H, m), 1.14 (6H, s), 1.13 (1H, m), 0.51 (2H, m), 0.42 (2H, m).

Step 3: Using the procedure of Preparation 7, Step 3, reaction of the product of Step 2 with NaN_3 afforded Preparation 9. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (2H, m), 6.67 (2H, m), 4.42 (2H, bs), 1.16 (1H, m), 1.15 (6H, s), 0.49 (2H, m), 0.42 (2H, m).

Preparation 10



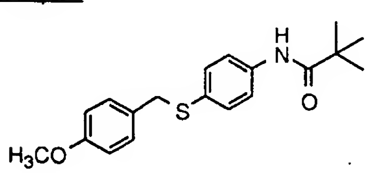
Step 1:



A mixture of 4-fluoronitrobenzene (10.0 g, 70.9 mmol), 4-methoxybenzylmercaptan (14.8 mL, 106 mmol), and K_2CO_3 (19.6 g, 142 mmol) in acetone (150 mL) was refluxed for 4h. The cooled reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3x100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford an oil (17.1 g, 87%) that was used without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (m, 2H, ArH), 7.38 (m, 4H, ArH), 6.94 (m, 2H, ArH), 4.28 (s, 2H, -CH_2-), 3.87 (s, 3H, CH_3O-).

Step 2: Reduction of the product from Step 1 (17 g, 62 mmol) with $NiCl_2.6H_2O$/ $NaBH_4$ according to the procedure of Preparation 6, step 2, gave the product aniline (6.67 g, 44%). ^1H Nmr ($CDCl_3$, 400 MHz) δ 7.18 (m, 4H, ArH), 6.82 (m, 2H, ArH), 6.61 (m, 2H, ArH), 3.95 (s, 2H, -CH_2-), 3.85 (s, 3H, CH_3O-).

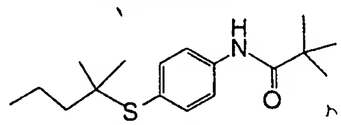
Step 3:



A mixture of the product of Step 2 (6.67 g, 27.2 mmol), trimethylacetyl chloride (5.0 mL, 40 mmol), and DMAP (6.64 g, 54.4 mmol) in CH_2Cl_2 (100 mL) was stirred for 0.3 h. Then CH_2Cl_2 (200 mL) was added and the mixture was washed with 1M HCl. The organic layer was dried (Na_2SO_4), filtered, and evaporated. Recrystallization of the residue from Et_2O/hexane/CH_2Cl_2 afforded the product (4.6 g, 51%) as a white solid. MS (Cl) *m/e* 330 $(M+H)^+$.

Step 4: To a stirred, ice-cold mixture of the product of Step 3 (500 mg, 1.46 mmol) in CH_2Cl_2 (25 mL), was added CF_3COOH (6 mL) and $Hg(OAc)_2$ (465 mg, 1.46 mmol). After 1.3 h, the reaction mixture was poured into H_2O, aqueous Na_2S was added, and the mixture was extracted with 1:2 EtOAc/hexanes. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was subjected to flash chromatography (1:2 EtOAc/hexanes) to give the product (305 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (m, 2H, ArH), 7.33 (m, 2H, ArH), 1.49 (s, 3H, $(CH_3)_3$-).

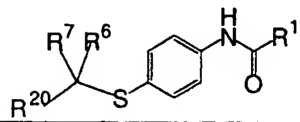
Example 1

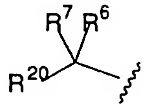
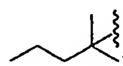
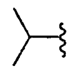
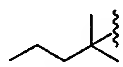
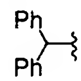
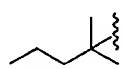
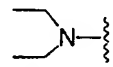
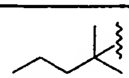
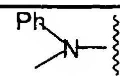
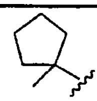
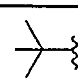
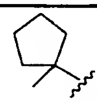
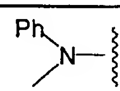
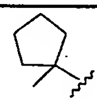
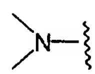
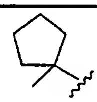
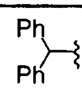
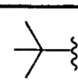
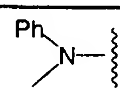
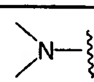
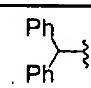
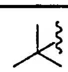
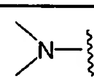


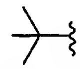
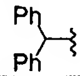
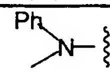
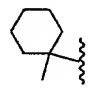
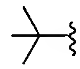
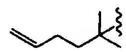
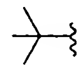
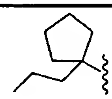
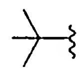
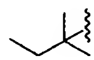
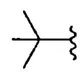
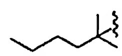
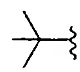
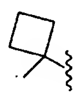
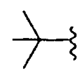
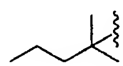
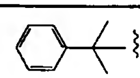
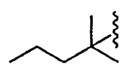
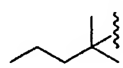
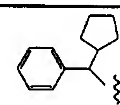
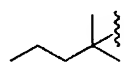
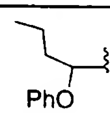
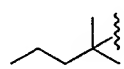
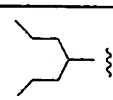
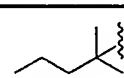
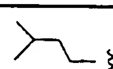
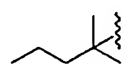
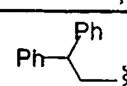
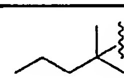
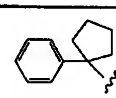
To a mixture of Preparation 1 (10.00 g, 47.7 mmol) and pyridine (7.70 ml, 95.5 mmol) in CH_2Cl_2 (100 ml) was added trimethylacetyl chloride (8.80 ml, 71.6 mmol). The reaction mixture was stirred at RT for 0.5 h, then poured into 2 M HCl (100 ml). The mixture was extracted with CH_2Cl_2 (3x100 ml), dried (Na_2SO_4), filtered, and concentrated. The residue was subjected to flash column chromatography (1:10 EtOAc/hexanes) to afford the title compound (76%). ^{1}H NMR ($CDCl_3$, 400 M Hz) δ 7.50–7.39 (m, 4H, ArH), 7.32 (S, 1H, NH), 1.50–1.35 (m, 4H, CH_2CH_2), 1.29 (s, 9H, $(CH_3)_3C$), 1.17 (s, 6H, $(CH_3)_2C$), 0.88 (t, 3H, CH_3CH_2). MS (Cl) *m/e* 294 $(M+H)^+$.

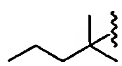
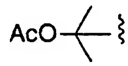
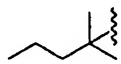
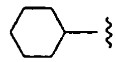
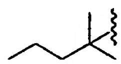
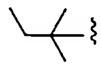
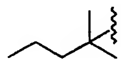
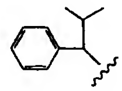
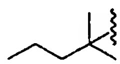
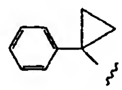
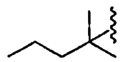
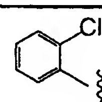
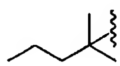
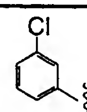
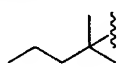
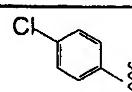
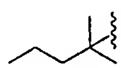
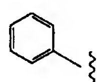
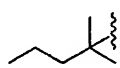
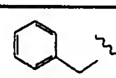
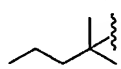
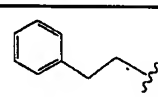
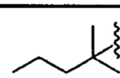
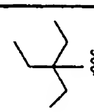
Using appropriate starting materials and essentially the same procedure the following compounds can be prepared (Table 1).

Table 1

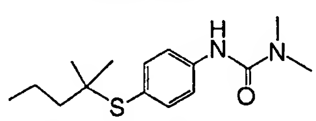


Ex.		R1	*m/e* CI (M+H)+
1A			280
1B			404
1C			309
1D			343
1E			292
1F			341
1G			279
1H			402
1I			294
1J			343
1K			281
1L			404
1M			253

1N			266
1O			376
1P			315
1Q			306
1R			306
1S			320
1T			280
1U			308
1V			278
1W			356
1X			322
1Y			396
1Z			386
1AA			336
1AB			308
1AC			418
1AD			382

1AE			338
1AF			320
1AG			308
1AH			370
1AI			354
1AJ			348
1AK			348
1AL			348
1AM			314
1AN			328
1AO			342
1AP			336

Example 2

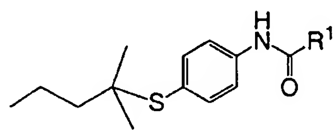


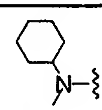
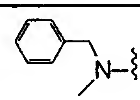
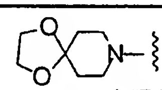
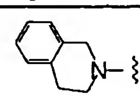
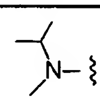
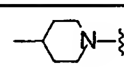
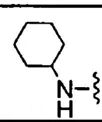
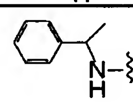
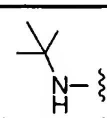
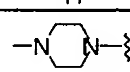
A mixture of Preparation 1 (1.03 g, 4.92 mmol), Et_3N (3.40 ml, 24.6 mmol) and triphosgene (0.585 g, 1.97 mmol) in toluene (60 ml) was refluxed for 2 h, then allowed to cool to RT. $(CH_3)_2NH$ (2.0 M in THF) (4.90 ml, 9.84 mmol) was added. The reaction mixture was allowed to stir at RT for 1.5 h, then poured into cold water. The whole was extracted

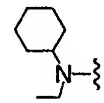
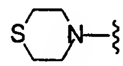
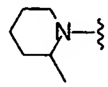
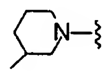
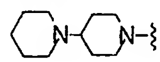
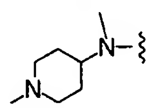
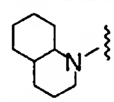
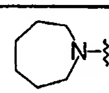
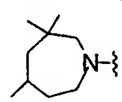
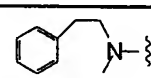
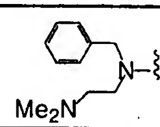
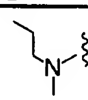
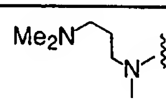
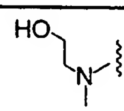
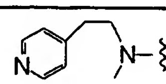
with CH_2Cl_2 (3x100 ml), dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (1:1 EtOAc/hexanes) afforded the title compound (1.03 g, 74%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 M Hz) δ 7.43 (m, 4H, <u>ArH</u>), 6.39 (s, 1H, <u>NH</u>CO), 3.07 (s, 6H, N($\underline{CH_3}$)$_3$), 1.45 (m, 4H, $\underline{CH_2CH_2}CMe_2S$), 1.23 (s, 6H, $(\underline{CH_3})_2CS$), 0.93 (t, 3H, J=6.88 Hz, $\underline{CH_3}CH_2$). MS (CI) *m/e* 281 $(M+H)^+$.

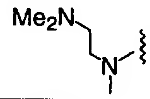
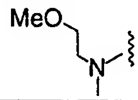
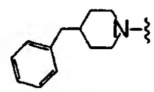
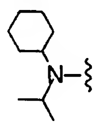
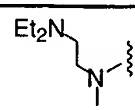
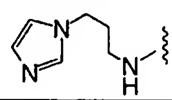
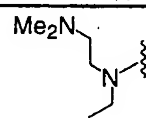
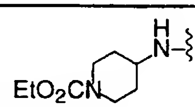
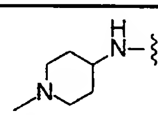
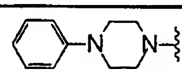
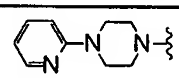
Using appropriate starting materials and essentially the same procedure the following compounds can be prepared (Table 2).

Table 2

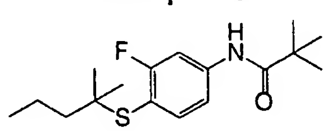


Ex.	R^1	*m/e* CI $(M+H)^+$
2A		349
2B		357
2C		379
2D		369
2E		309
2F		335
2G		335
2H		357
2I		309
2J		336

2K		363
2L		339
2M		335
2N		335
2O		372
2P		404
2Q		364
2R		375
2S		335
2T		377
2U		371
2V		414
2W		309
2X		352
2Y		311
2Z		372

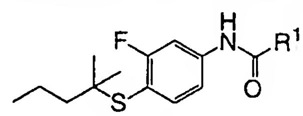
2AA		338
2AB		325
2AC		411
2AD		377
2AE		366
2AF		361
2AG		352
2AH		408
2AI		350
2AJ		398
2AK		399

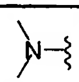
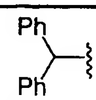
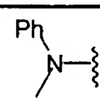
Example 3



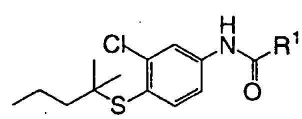
To an ice-cold mixture of Preparation 2 (2.32 g, 9.03 mmol) and $NiCl_2 \cdot 6H_2O$ (4.83 g, 20.3 mmol) in CH_3OH (100 ml) was added $NaBH_4$ (1.53 g, 40.6 mmol) in portions. After 1.5 h, the reaction mixture was poured into water and the whole was extracted with CH_2Cl_2 (3x100 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and

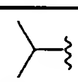
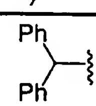
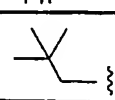
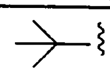
concentrated in vacuo to give the desired 3-fluoro-4-(1',1'-dimethyl-butylthio)aniline (56%). A mixture of the aniline (60 mg, 0.264 mmol), pyridine (0.11 ml, 1.32 mmol), and $(CH_3)_3CCOCl$ (0.065 ml, 0.528 mmol) in CH_2Cl_2 (1.0 ml), was stirred overnight, then subjected to plc (1:6 EtOAc/hexanes) to give the title compound (41%). ^1H NMR ($CDCl_3$, 400 M Hz) δ 7.65 (m, 1H, ArH), 7.45 (m, 2H, ArH & NH), 7.20 (m, 1H, ArH), 1.52(m, 4H, $CH_3\underline{CH_2CH_2}$), 1.37(s, 9H, $C(\underline{CH_3})_3$), 1.27(s, 6H, $C(\underline{CH_3})_2S$), 0.96 (t, 3H, J=6.8 Hz, $\underline{CH_3}CH_2CH_2$). MS (CI) *m/e* 312 $(M+H)^+$. Similarly prepared were compounds of the formula:

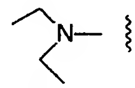
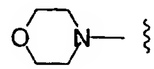
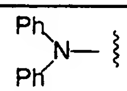


Ex.	R^1	*m/e* CI $(M+H)^+$
3A		299
3B		422
3C		361

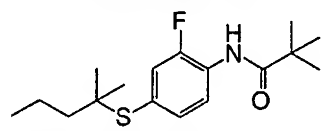
Using the compound of Preparation 3 and the appropriate acid chloride or carbamyl chloride, the procedure of Example 3 afforded the following compounds:



Ex.	R^1	*m/e* CI $(M+H)^+$
3D		314
3E		438
3F		342
3G		328

3H		343
3I		357
3J		439

Example 4



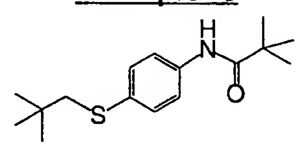
Step 1: A mixture of 2,4-difluoronitrobenzene (2.6 ml, 23.3 mmol), *p*-methoxybenzyl mercaptan (2.00 g, 11.7 mmol), K_2CO_3 (6.47 g, 46.8 mmol) in acetone (50 ml) was refluxed for 20 h. The reaction mixture was poured into cold water. The whole was extracted with CH_2Cl_2 (3x100 ml), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (1:30→1:20 EtOAc/hexanes) to give the desired 2-fluoro-4-(4'-methoxybenzylmercapto)nitrobenzene containing a small amount of 4-fluoro-2-(4'-methoxybenzylmercapto)nitrobenzene. MS (CI) *m/e* 294 $(M+H)^+$.

Step 2: To a vigorously stirred ice-cold mixture of 2-fluoro-4-(4'-methoxy-benzylmercapto)nitrobenzene and $NiCl_2{\bullet}6H_2O$ (6.08 g, 25.6 mmol) in CH_3OH was added $NaBH_4$ (1.93 g, 51.1 mmol) in portions. The reaction mixture was stirred for 1 h at 0 °C, then poured into cold water. The whole was extracted with CH_2Cl_2 (3x100 ml) and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give 2-fluoro-4-(4'-methoxybenzylmercapto)aniline. MS (CI) *m/e* 264 $(M+H)^+$.

Step 3: A mixture of the product of step 2, pyridine (3.1 ml, 38.4 mmol) and $(CH_3)_3CCOCl$ (3.2 ml, 25.6 mmol) in CH_2Cl_2 (100 ml) was stirred for 2 h, then poured into cold water. The whole was extracted with CH_2Cl_2 (3x100 ml) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford 2-fluoro-4-(4'-methoxybenzyl-mercapto)phenyl-2,2-dimethylpropanamide. MS (CI) *m/e* 348 $(M+H)^+$.

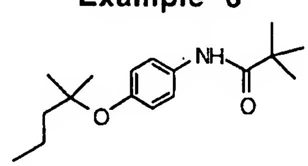
Step 4: A solution of the product of Step 3 in CF_3CO_2H (20 ml) was heated at 80 °C for 28 h, then concentrated. The residue (963 mg) was dissolved in Et_2O (2 ml). 2-Methyl-1-pentene (2.0 ml) and concentrated H_2SO_4 (0.5 ml) were added with stirring. After 20 min. the reaction mixture was poured into CH_2Cl_2 (200 ml), and washed with water and sat'd NaCl. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by plc (1:10 EtOAc/hexanes) to afford the title compound in 16% overall yield starting from 2,4-difluoro-nitrobenzene. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.37 (t, 1H, J=8.5 Hz, ArH), 7.71 (s, 1H, NH), 7.30 (m, 2H, ArH), 1.50 (m, 4H, $CH_3\underline{CH_2CH_2}$), 1.37 (s, 9H, $C(\underline{CH_3})_3$), 1.25 (s, 6H, $C(\underline{CH_3})_2S$), 0.95 (t, 3H, J=7.0 Hz, $\underline{CH_3}CH_2CH_2$). MS(CI) *m/e* 312 $(M+H)^+$.

Example 5



To a refluxing suspension of $FeSO_4.7H_2O$ (3.95 g, 14.2 mmol) and Fe powder (397 mg, 7.1 mmol) in 1:1 H_2O/EtOH (100 ml) was added a hot solution of Preparation 4 (319 mg, 1.42 mmol) in EtOH (10 ml). The suspension was refluxed for 6h, allowed to cool, and filtered through celite. The filtrate was extracted with CH_2Cl_2 and the organic extract was dried (Na_2SO_4), filtered, and concentrated to afford the aniline (185 mg). A portion of the aniline (30 mg, 0.15 mmol), trimethylacetyl chloride (47 mg, 0.38 mmol), pyridine (62 mg, 0.77 mmol), and 4-dimethylamino-pyridine (19 mg, 0.15 mmol) in CH_2Cl_2 (2 ml) was stirred overnight. The reaction mixture was subjected to flash chromatography (1:10 EtOAc/hexanes) to afford the title compound (37 mg, 95%) as white solid. MS (CI) *m/e* 280 $(M+H)^+$.

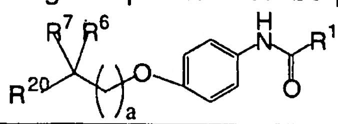
Example 6

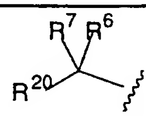
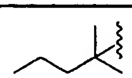
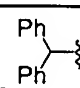
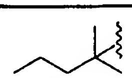
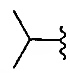
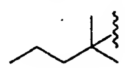
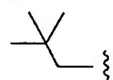
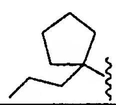
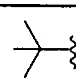
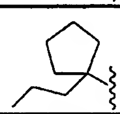
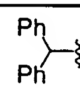
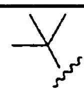
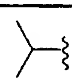
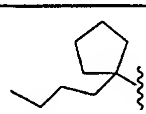
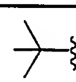
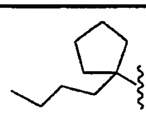
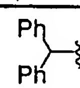
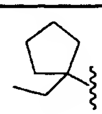
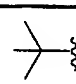
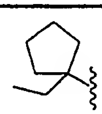
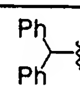


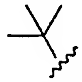
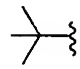
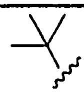
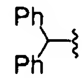
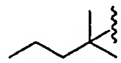
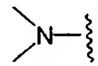
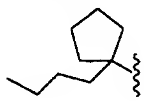
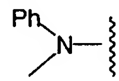
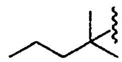
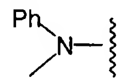
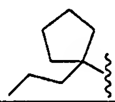
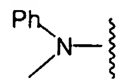
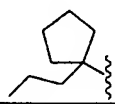
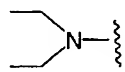
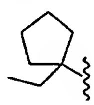
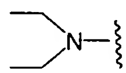
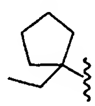
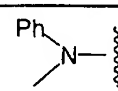
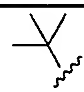
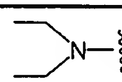
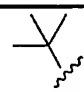
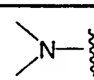
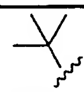
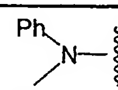
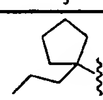
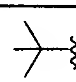
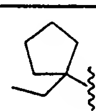
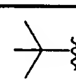
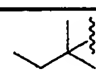
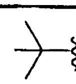
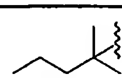
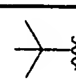
Using the procedure of Example 1, the reaction of Preparation 5 (97 mg, 0.5 mmol) and trimethylacetyl chloride (0.12 ml, 1.0 mmol) afforded the title compound (137 mg, 99%) as a white solid. ^1H NMR

($CDCl_3$, 400 MHz) δ 7.43 (2H, m, ArH), 6.97 (2H, m, ArH), 1.64 - 1.48 (4H, m, $-CH_2CH_2-$), 1.34 (9H, s, $-C(CH_3)_3$), 1.28 (6H, s, $-OC(CH_3)_2-$), 0.97 (3H, t, $J = 7.1$ Hz, $-CH_2\underline{CH_3}$). MS (CI) *m/e* 278 $(M+H)^+$.

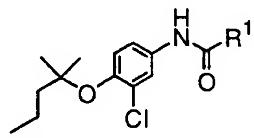
Using appropriate starting materials and essentially the same procedure, the following compounds can be prepared:



Ex.		a	R^1	*m/e* CI $(M+H)^+$
6A		0		388
6B		0		264
6C		0		292
6D		0		304
6E		0		414
6F		1		250
6G		0		318
6H		0		428
6I		0		290
6J		0		400

6K		1		264
6L		1		374
6M		0		265
6N		0		367
6O		0		327
6P		0		353
6Q		0		319
6R		0		305
6S		0		339
6T		1		279
6U		1		251
6V		1		313
6W		1		317
6X		1		303
6Y		1		277
6Z		1		291

The following compounds can also be prepared using appropriate starting materials and similar methods:



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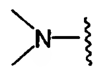
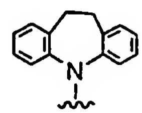
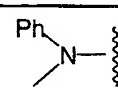
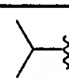
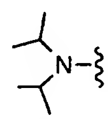
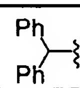
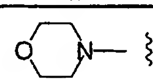
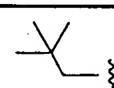
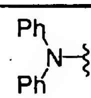
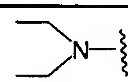
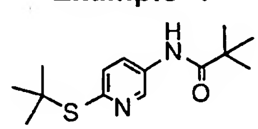
6AA		299
6AB		449
6AC		361
6AD		298
6AE		355
6AF		422
6AG		341
6AH		326
6AI		423
6AJ		327

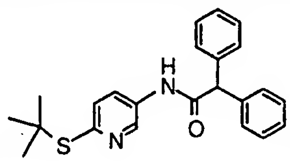
Example 7

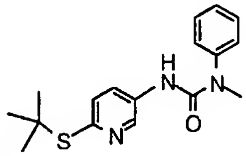


Using the procedure of Example 1, the reaction of the product of Preparation 6 (21 mg, 0.11 mmol) and trimethylacetyl chloride (25 µl, 0.20 mmol) afforded the title compound (20 mg, 65%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (1H, s, ArH), 8.17 (1H, d, J = 8.6 Hz,

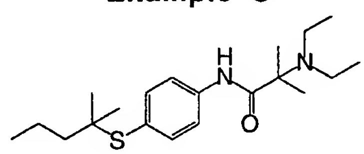
ArH), 7.47 (1H, d, J = 8.6 Hz, ArH), 1.49 (9H, s, $-CO(CH_3)_3$), 1.30 (9H, s, $-S(CH_3)_3$). MS (CI) *m/e* 267 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure the following compounds can be prepared:

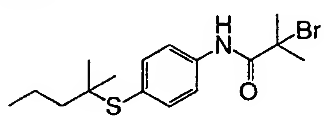
7A)  MS (CI) *m/e* 377 $(M+H)^+$.

7B)  MS (CI) *m/e* 316 $(M+H)^+$.

Example 8



Step 1:



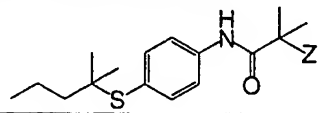
13

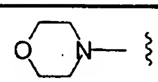
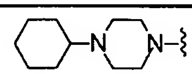
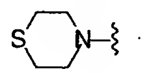
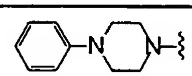
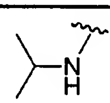
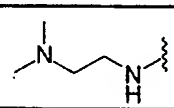
To a mixture of Preparation **1** (2.00 g, 9.55 mmol) and pyridine (1.50 ml, 19.1 mmol) in CH_2Cl_2 (100 ml) was added 2-bromoisobutyryl bromide (1.80 ml, 14.3 mmol). The reaction mixture was stirred at RT for 15 min, then poured into 1N HCl and extracted with CH_2Cl_2 (3x100 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was subjected to flash chromatography (1:10 EtOAc/hexanes) to afford **13** (99%) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.55 (s, 1H, <u>NH</u>CO), 7.55 (m, 4H, <u>ArH</u>), 2.10 (s, 6H, $(CH_3)_2CBr$), 1.51 (m, CH_2CH_2), 1.26 (s, 6H, $(CH_3)_2CS$), 0.96 (t, 3H, CH_3CH_2). MS (CI) *m/e* 358 $(M+H)^+$.

Step 2: To a stirred solution of Et_2NH (58 μl, 0.558 mmol) in THF (2.0 ml) was added NaH (8.0 mg, 0.307 mmol), followed by **13** (100 mg, 0.279 mmol). The reaction mixture was stirred at RT for 30 min. and then subjected directly to plc (1:15 EtOAc/hexanes) to afford the title

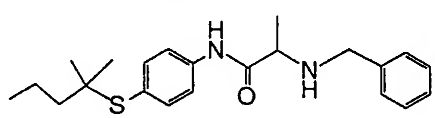
compound (61%). [1]H NMR ($CDCl_3$, 400 M Hz) δ 9.63 (s, 1H, NHCO), 7.52 (m, 4H, <u>ArH</u>), 2.62 (q, 4H, J=7.15 Hz, $N(\underline{CH_2}CH_3)_2$), 1.48 (m, 4H, $\underline{CH_2CH_2}CMe_2S$), 1.36 (s, 6H, $(\underline{CH_3})_2CN$), 1.24 (s, 6H, $(\underline{CH_3})_2CS$), 1.17 (t, 6H, J=7.09 Hz, $N(CH_2\underline{CH_3})_2$), 0.94 (t, 3H, J=6.88 Hz, $\underline{CH_3}(CH_2)_2CMe_2S$). MS (CI) *m/e* 351 $(M+H)^+$.

Using the same procedure and the appropriate amine, the following compounds were also prepared:

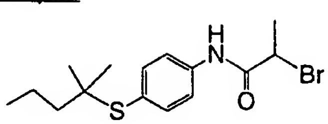


Ex.	Z	*m/e* CI $(M+H)^+$
8A		365
8B		446
8C		381
8D		440
8E		337
8F		366

Example 9



<u>Step 1</u>:

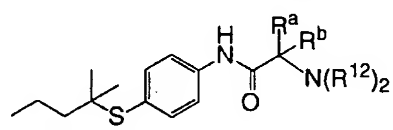
 **14**

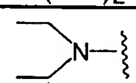
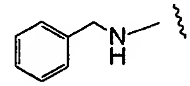
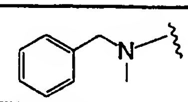
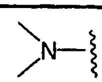
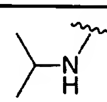
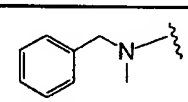
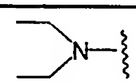
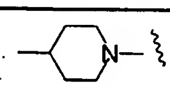
Using the product of Preparation **1** (210 mg, 1.0 mmol) and 2-bromo-propionyl bromide (0.10 ml, 1.0 mmol) as starting materials, the procedure described for **13** (Example 8, Step 1) afforded **14** (218 mg, 64%). [1]H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, bs, NH), 7.55 (4H, m, ArH), 4.61 (1H, q, *J* = 7 Hz, $-C\underline{H}CH_3$), 2.03 (3H, d, *J* =7 Hz, $-CH\underline{CH_3}$),

1.60-1.45 (4H, m, $\underline{CH_2CH_2}CH_3$), 1.26 (6H, s, $(\underline{CH_3})_2C$), 0.97 (t, 3H, J=7 Hz, $CH_2\underline{CH_3}$).

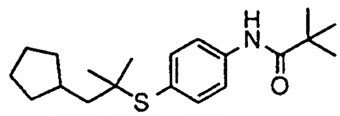
Step 2: A mixture of **14** (102 mg, 0.30 mmol), benzylamine (65 µl, 0.59 mmol), and K_2CO_3 (83 mg, 0.60 mmol) in DMSO (1 ml) was stirred. After 2 h, H_2O (10 ml) was added and the whole was extracted with CH_2Cl_2. The combined organic layers were washed with sat'd NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was subjected to plc (1:1 EtOAc/ hexanes) to afford the title compound (70 mg, 62%) as a glass. ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (1H, bs, NH), 7.62 (2H, m, ArH), 7.52 (2H, m, ArH), 7.48-7.30 (5H, m, ArH), 3.90 (2H, s, $\underline{CH_2}Ph$), 3.51 (1H, m, $-C\underline{H}CH_3$), 1.60-1.45 (7H, m, $-CH\underline{CH_3}$, $\underline{CH_2CH_2}CH_3$), 1.26 (6H, s, $(\underline{CH_3})_2C$), 0.97 (t, 3H, J=7 Hz, $CH_2\underline{CH_3}$). MS (CI) *m/e* 371 (M+H)+.

Using the appropriate amine and essentially the same procedures, the following compounds can also be prepared:



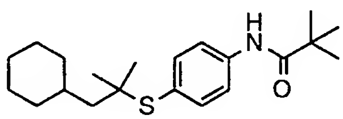
Ex.	R^a	R^b	$N(R^{12})_2$	*m/e* CI $(M+H)^+$
9A	H	H		323
9B	H	H		357
9C	H	H		371
9D	CH_3	H		309
9E	CH_3	H		323
9F	CH_3	H		385
9G	CH_3	H		337
9H	CH_3	H		363

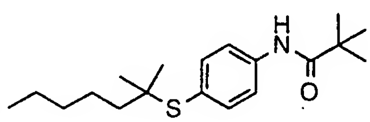
Example 10



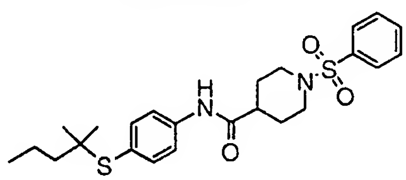
To a solution of Preparation 10 (50 mg, 0.24 mmol) and 3-cyclopentyl-2-methylprop-1-ene (59 mg, 0.48 mmol) in Et_2O (0.5 ml) was added conc. H_2SO_4 (26 µl, 0.48 mmol). The reaction mixture was stirred for 18 h, then subjected to plc (1:6 EtOAc/hexanes) to give the product (28 mg, 35%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (m, 4H, ArH), 7.45 (s, 1H, NH), 2.13 (m, 1H, aliphatic H), 1.96 (m, 2H, aliphatic H), 1.62 (m, 4H, aliphatic H), 1.41 (s, 9H, $(CH_3)_3C$-), 1.31 (s, 6H, $(CH_3)_2C$), 1.19 (m, 4H, aliphatic). MS (CI) *m/e* 334 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure the following compounds are prepared.

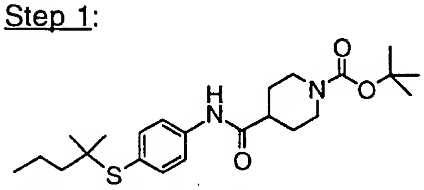
10A)  MS (CI) *m/e* 348 $(M+H)^+$.

10B)  MS (CI) *m/e* 322 $(M+H)^+$.

Example 11



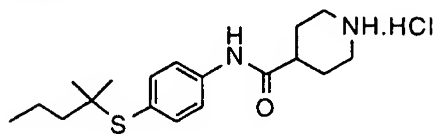
Step 1:



To a mixture of Preparation 1 (2.00 g, 9.56 mmol) and N-t-butoxy-carbonylpiperidine-4-carboxylic acid (2.40 g, 10.5 mmol) in DMF (50 ml) was added DMAP (0.082 g, 0.67 mmol) and EDC (1.83 g, 11.6 mmol). The reaction mixture was stirred at RT for 16 h, then partitioned between H_2O (300 ml) and EtOAc (300 ml). The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and evaporated. The residue was

subjected to flash chromatography (1:5 EtOAc/ hexanes) to afford the product (2.16 g, 54%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (4H, m, ArH), 7.26 (1H, s, -NH), 4.23 (2H, m, $-CH_2$), 2.83 (2H, m, $-CH_2$), 2.42 (1H, m, -CH), 1.93 (2H, m, $-CH_2$), 1.78 (2H, m, $-CH_2$), 1.50 (9H, s, $-C(CH_3)_3$), 1.50-1.42 (4H, m, $-(CH_2)_2-$), 1.23 (6H, s, $(CH_3)_2C-$), 0.94 (3H, t, $J = 7.3$ Hz, CH_3).

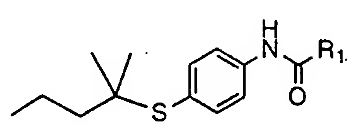
Step 2:

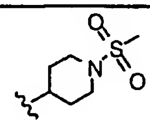
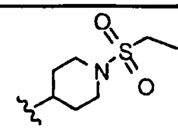
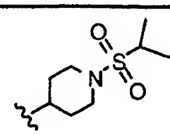
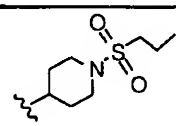
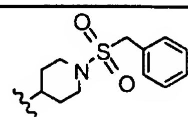
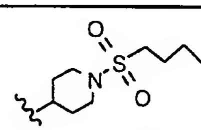
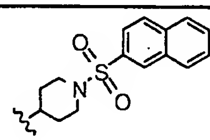
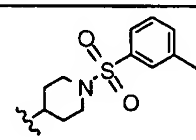
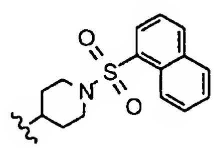
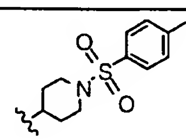
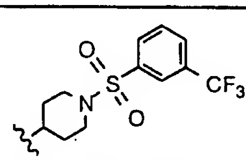


To the product of Step 1 (2.16 g, 5.1 mmol) was added 4M HCl in 1,4-dioxane (70 ml) and the reaction mixture was stirred for 0.5 h. The mixture was concentrated under reduced pressure to afford a white solid (1.80 g) that was used without further purification. ^{1}H NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ 7.45 (4H, m, ArH), 3.32 (2H, m, $-CH_2$), 3.06 (2H, m, $-CH_2$), 2.71 (1H, m, -CH), 2.02 (2H, m, $-CH_2$), 1.91 (2H, m, $-CH_2$), 1.45-1.32 (4H, m, $-(CH_2)_2-$), 1.14 (6H, s, $(CH_3)_2C-$), 0.84 (3H, t, $J = 7.3$ Hz, CH_3).

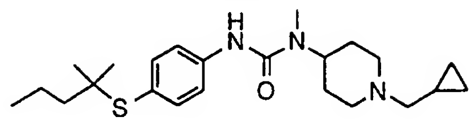
Step 3: To a mixture of the product of Step 2 (0.10 g, 0.28 mmol) and Et_3N (0.06 ml, 0.43 mmol) in CH_2Cl_2 (1.5 ml) was added benzene-sulfonyl chloride (63 mg, 0.36 mmol). The reaction mixture was stirred for 3 days, then diluted with CH_2Cl_2. The mixture was washed with 10% NH_4OH, 1M HCl, and saturated NaCl, then dried ($MgSO_4$), filtered and evaporated. The residue was subjected to plc (1:99 CH_3OH/CH_2Cl_2) to afford the product (90 mg, 70%) as a white solid. Anal. calcd for $C_{24}H_{32}N_2O_3S_2$: C, 62.58; H, 7.00; N, 6.08; S, 13.92. Found: C, 62.20; H, 7.05; N, 6.07; S, 13.72%. MS (FAB) *m/e* 461 $(M+H)^+$.

Using the appropriate sulfonyl chloride starting material and the procedure of Step 3, the following compounds were prepared:

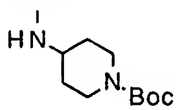


Ex.	R^1	m/e CI $(M+H)^+$
11A		399
11B		413
11C		427
11D		427
11E		475
11F		441
11G		511
11H		475
11I		511
11J		475
11K		529

Example 12

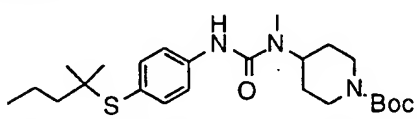


Step 1:



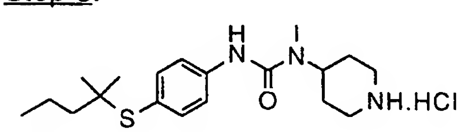
To a mixture of N-t-butoxycarbonyl-4-piperidone (10.0 g, 0.050 mol) and aqueous CH_3NH_2 (40% w/w, 10 ml) in 1,2-dichloroethane (125 ml) was added $NaBH(OAc)_3$ (16.0 g, 0.075 mol). The reaction mixture was stirred overnight, then 1M NaOH (250 ml) was added and the whole was extracted with Et_2O (700 ml). The organic layer was washed with sat'd NaCl, dried ($MgSO_4$), filtered, and concentrated to give the product (10.5 g, 97%) as an oil that was used directly in Step 2. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.09 (2H, m), 2.86 (2H, m), 2.55 (1H, m), 2.50 (3H, s), 1.90 (2H, m), 1.51 (9H, s), 1.30 (2H, m).

Step 2:



Using the procedure of Example 2, the product of Step 1, triphosgene, and the product of Preparation 1 were reacted to give the product. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (4H, m, ArH), 6.32 (1H, s, NH), 4.35 (1H, m, CH), 4.15 (2H, m, CH_2), 2.81 (3H, s, NCH_3), 2.73 (2H, m, CH_2), 1.65-1.32 (8H, m, CH_2x4), 1.90 (2H, m), 1.40 (9H, s, $C(CH_3)_3$), 1.13 (6H, s, $(CH_3)_2$), 0.83 (3H, t, $J = 6.9$ Hz, CH_3).

Step 3:



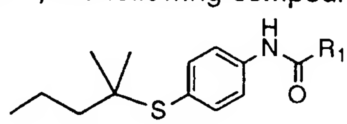
Using the procedure of Example 11, Step 2, the product of Step 2 was reacted with 4M HCl in 1,4-dioxane to give the product. ^1H NMR (CD_3OD, 400 MHz) δ 7.38 (4H, m, ArH), 4.38 (1H, m, CH), 3.50 (2H, m, CH_2), 3.12 (2H, m, CH_2), 2.96 (3H, s, NCH_3), 2.03 (2H, m, CH_2), 1.93

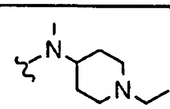
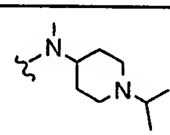
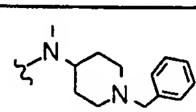
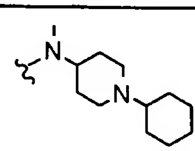
(2H, m, CH_2), 1.55-1.38 (4H, m, CH_2x2), 1.18 (6H, s, $(CH_3)_2$), 0.91 (3H, t, $J = 7.2$ Hz, CH_3).

Step 4: To a suspension of the product of Step 3 (200 mg, 0.52 mmol) and $NaBH(OAc)_3$ (155 mg, 0.73 mmol) in 1,2-dichloroethane (2.5 ml) was added cyclopropane carboxaldehyde (0.12 ml, 1.6 mmol). After stirring for 16 h, the reaction mixture was added to 1M NaOH (10 ml) and extracted with CH_2Cl_2 (20 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was subjected to plc (1:9 CH_3OH/CH_2Cl_2 saturated with conc. NH_4OH) to afford the product (166 mg, 79%) as a white solid. Anal. calcd for $C_{23}H_{37}N_3OS$: C, 68.44; H, 9.24; N, 10.41; S, 7.94. Found: C, 68.09; H, 9.18; N, 10.36; S, 7.56%. MS (CI) *m/e* 404 $(M+H)^+$.

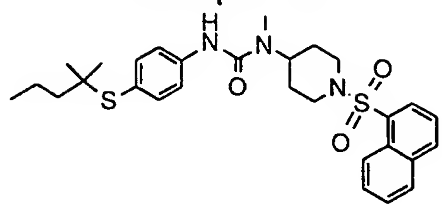
Treatment of the product with excess 1M HCl in Et_2O followed by evaporation of the Et_2O under reduced pressure gave the HCl salt. Anal. calcd for $C_{23}H_{38}N_3OSCl \cdot 0.5H_2O$: C, 61.38; H, 8.96; N, 9.34; S, 7.12. Found: C, 61.72; H, 8.65; N, 9.30; S, 6.81%.

Using the appropriate ketone or aldehyde starting material and the procedure of step 4, the following compounds were prepared:



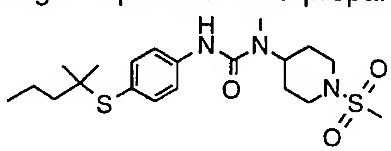
Ex.	R^1	*m/e* CI $(M+H)^+$
12A		378
12B		392
12C		440
12D		432

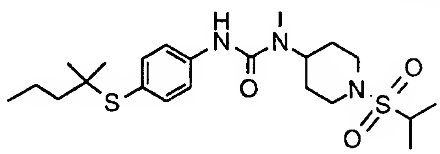
Example 13

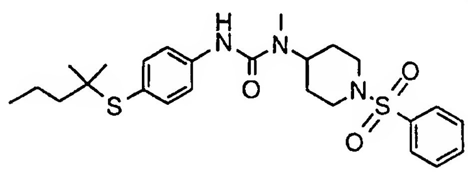


Using the procedure of Example 11, Step 3, reaction of the product of Example 12, Step 3 with 1-naphthalenesulfonyl chloride afforded the product. Anal. calcd for $C_{23}H_{37}N_3OS{\cdot}0.25H_2O$: C, 64.03; H, 6.90; N, 7.70; S, 11.88. Found: C, 63.75; H, 6.77; N, 7.70; S, 12.05%. MS (CI) *m/e* 540 $(M+H)^+$.

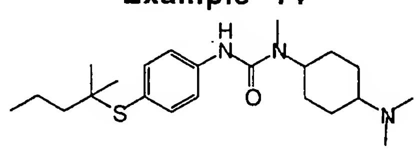
Using the appropriate sulfonyl chloride starting material, the following compounds were prepared:

13A)  MS (CI) *m/e* 428 $(M+H)^+$.

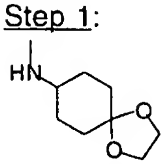
13B)  MS (CI) *m/e* 456 $(M+H)^+$.

13C)  MS (CI) *m/e* 490 $(M+H)^+$.

Example 14



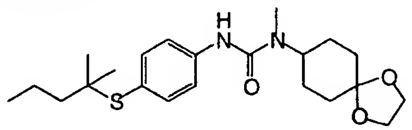
Step 1:



To a stirred mixture of 1,4-cyclohexanedione monoethylene ketal (4.68 g, 30 mmol) and 40% w/w aq. CH_3NH_2 (6.0 ml) in 1,2-dichloroethane (75 ml), was added $Na(OAc)_3BH$ (9.6 g, 45 mmol) in portions.

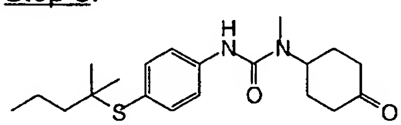
The reaction mixture was vigorously stirred for 16 h, then 1N NaOH (75 ml) was added. The organic layer was washed with sat'd NaCl, dried ($MgSO_4$), filtered and evaporated to give an oil (4.60 g, 90%) that was used without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.97 (4H, s), 2.47 (1H, m), 2.46 (3H, s), 1.91 (2H, m), 1.80 (2H, m), 1.59 (2H, m), 1.45 (2H, m).

Step 2:



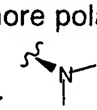
Using the procedure of Example 2, reaction of the product of Step 1 with the isocyanate derived from Preparation 1 afforded the product. MS *m/e* 407 $(M+H)^+$.

Step 3:



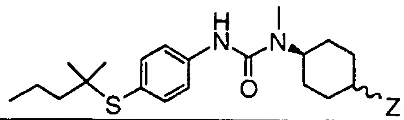
A mixture of the product of Step 2 (1.13 g, 2.8 mmol) and 3M HCl (10 ml) in THF (20 ml) was stirred at RT for 1 h. The reaction mixture was neutralized with 1M NaOH and extracted with CH_2Cl_2 (2x50 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (1:99 CH_3OH/CH_2Cl_2) of the residue afforded the product (0.90 g, 88%). MS *m/e* 363 $(M+H)^+$.

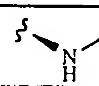
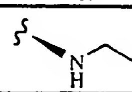
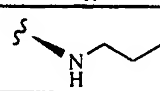
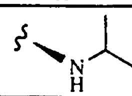
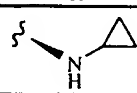
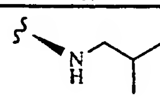
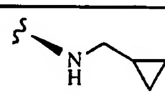
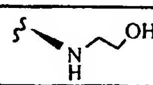
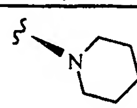
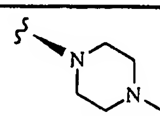
Step 4: To a stirred mixture of the product of Step 3 (100 mg, 0.28 mmol) and 40% w/w $(CH_3)_2NH$ (0.09 ml, 0.9 mmol) in CH_2Cl_2 (1 ml) was added $Na(OAc)_3BH$ (88 mg, 0.42 mmol). After 16 h, 1M NaOH (5 ml) was added and the whole was extracted with CH_2Cl_2 (2x10 ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by preparative tlc (1:7:92 conc. $NH_4OH/CH_3OH/CH_2Cl_2$) afforded the less polar *cis* isomer, 14A (48 mg, 45%) and the more polar *trans* isomer, 14B (31 mg, 29%).

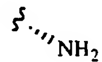
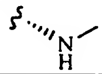
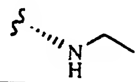
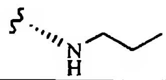
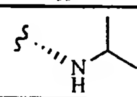
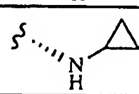
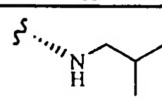
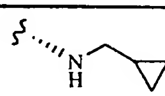
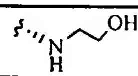
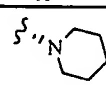
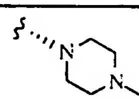
14A, *Cis* isomer  : ^1H NMR ($CDCl_3$+ CD_3OD, 400 MHz) δ 7.22 (4H, m), 4.08 (1H, m), 2.79 (3H, s), 2.13 (6H, s), 2.08 (1H, m), 1.83 (2H, m), 1.60 (2H, m), 1.40 – 1.23 (8H, m), 1.03 (6H, s), 0.74 (3H, t, J = 7.3 Hz). MS *m/e* 392 $(M+H)^+$.

14B, *Trans* isomer  : ^{1}H NMR ($CDCl_3$+ CD_3OD, 400 MHz) δ 7.22 (4H, m), 3.92 (1H, m), 2.72 (3H, s), 2.13 (6H, s), 1.96 (1H, m), 1.93 (2H, m), 1.63 (2H, m), 1.45 – 1.22 (8H, m), 1.04 (6H, s), 0.74 (3H, t, J = 7.2 Hz). MS m/e 392 $(M+H)^+$.

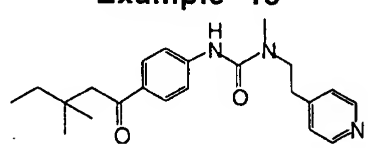
Using the appropriate amine and essentially the same procedure outlined in Example 14, Step 4, the following compounds were prepared.



Ex.	Z	*m/e*
14C		364
14D		378
14E		392
14F		406
14G		406
14H		404
14I		420
14J		418
14K		408
14L		432
14M		447

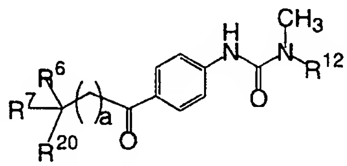
14N		434
14O		364
14P		378
14Q		392
14R		406
14S		406
14T		404
14U		420
14V		418
14W		408
14X		432
14Y		447

Example 15

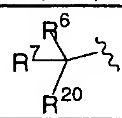
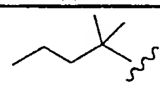
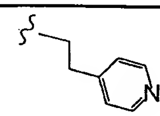
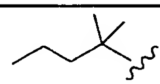
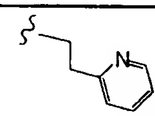
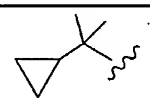
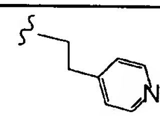
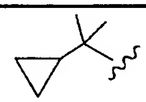
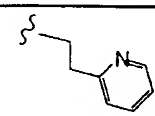
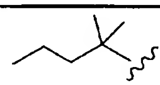
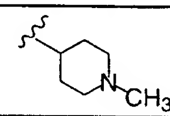
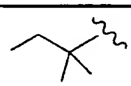
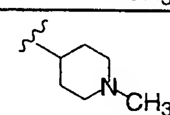
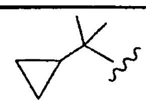
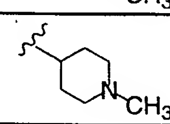
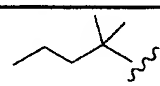
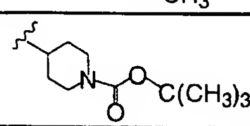
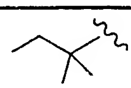
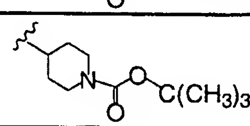
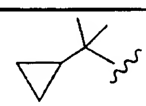
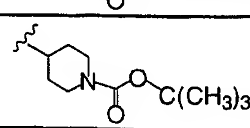


Using the procedure of Example 2, Preparation 7, *i*Pr_2NEt, triphosgene, and 4-(2-methylamino)ethylpyridine were reacted to give the product. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.50 (2H, s, <u>ArH</u>), 7.85 (2H, m, <u>ArH</u>), 7.41 (2H, m, <u>ArH</u>), 7.19 (2H, m, <u>ArH</u>), 6.60 (1H, s, <u>NH</u>), 3.60 (2H, t, *J* = 6.8 Hz, $\underline{CH_2}N$), 2.97 (3H, s, $\underline{CH_3}N$), 2.95 (2H, t, *J* = 7.2 Hz, $NCH_2\underline{CH_2}$), 2.77 (2H, s, $\underline{CH_2}CO$), 1.40 (2H, q, *J* = 7.6 Hz, $CH_3\underline{CH_2}$), 1.03 (6H, s, $\underline{(CH_3)_2C}$), 0.85 (3H, t, *J* = 7.6 Hz, $\underline{CH_3}CH_2$). MS (ES) *m/e* 368 $(M+H)^+$.

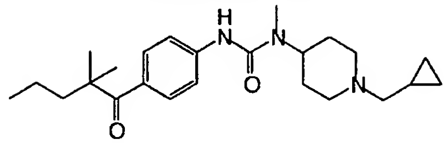
Reaction of Preparation 7,8, or 9, triphosgene, and the appropriate amine by essentially the same procedure afforded the following compounds:



wherein a, R^6, R^7, R^{20} and R^{12} are as defined in the table

Ex.		a	R^{12}	MS *m/e* (M+H)
15A		0		368
15B		0		368
15C		0		366
15D		0		366
15E		0		360
15F		1		360
15G		0		358
15H		0		446
15I		1		446
15J		0		444

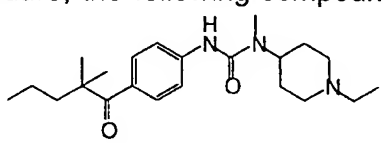
Example 16

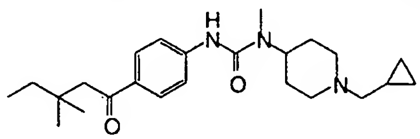


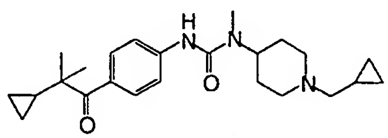
Step1: Using the procedure described in Example 11, Step 2, the compound of Example 15H was treated with HCl to obtain the hydrochloride. MS *m/e* 346 $(M-Cl)^+$.

Step 2: Using the procedure described in Example 12, Step 4, cyclopropane carboxaldehyde was reacted with the product of Step 1 to obtain the title compound. MS *m/e* 400 $(M+H)^+$.

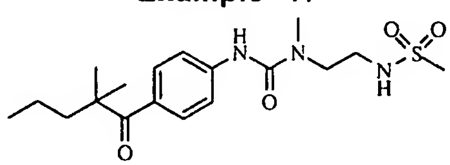
Using the appropriate starting materials and essentially the same procedure, the following compounds were prepared:

16A  MS *m/e* 374 $(M+H)^+$

16B  MS *m/e* 400 $(M+H)^+$

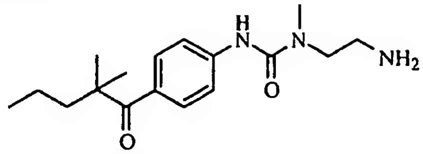
16C  MS *m/e* 398 $(M+H)^+$

Example 17



Step 1: To a mixture of t-butyldiphenylchlorosilane (9.3 g, 34 mmol) and Et_3N (5.12 g, 51 mmol) in CH_3CN (50 ml) was slowly added N-methyl-ethylenediamine (5.0 g, 67 mmol). The reaction mixture was stirred for 2 h. After removal of CH_3CN, the residue was dissolved in CH_2Cl_2 and washed with sat'd $NaHCO_3$ and H_2O. The organic layer was dried ($MgSO_4$), filtered and evaporated to give a colorless oil (10.2 g) which was used directly in Step 2.

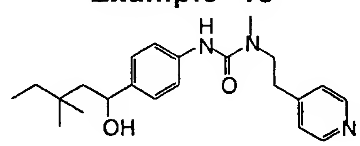
Step 2:



Using the procedure of Example 2, reaction of Preparation 8, triphosgene, and the product of Step 1 afforded the product. MS *m/e* 306.1 $(M+H)^+$.

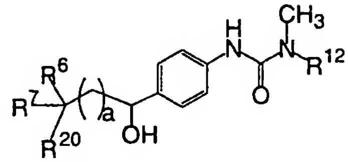
Step 3: To a solution of the product of Step 2 (95 mg, 0.31 mmol) and Et_3N (63 mg, 0.62 mmol) in CH_2Cl_2 (2 ml) was added CH_3SO_2Cl (72 mg, 0.63 mmol) dropwise. After 5 min, the reaction mixture was subjected to preparative TLC (CH_2Cl_2/CH_3OH/conc. NH_4OH 10:1:0.1) to afford the product (70 mg, 59%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.76 (2H, m, ArH), 7.47 (2H, m, ArH), 7.20 (1H, s, NH), 5.90 (1H, bs, NH), 3.50 (2H, m, $\underline{CH_2}CH_2$), 3.30 (2H, m, $CH_2\underline{CH_2}$), 2.98 (3H, s, CH_3), 2.97 (s, 3H, CH_3), 1.70 (m, 2H, CH_2), 1.05-1.4 (8H, m, $(CH_3)_2$ & CH_2), 0.9 (t, 3H, J = 7.3 Hz, CH_3). MS *m/e* 384.1 $(M+H)^+$.

Example 18

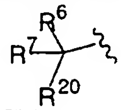
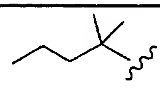
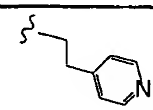
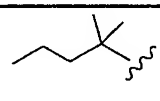
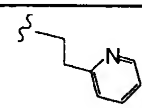
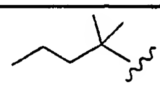
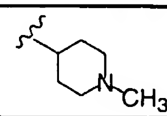
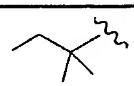
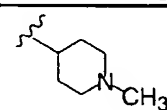
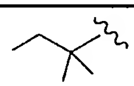
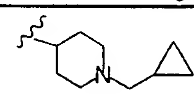
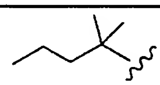
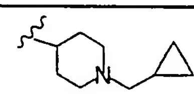
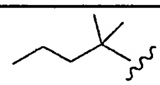
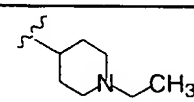
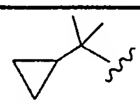
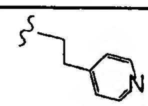
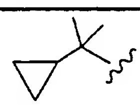
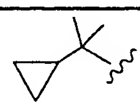
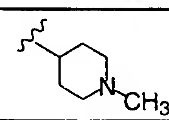
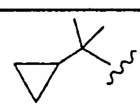
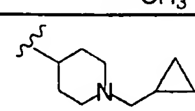
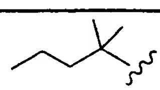
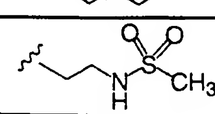


To a solution of Example 15 (330 mg, 0.90 mmol) in CH_3OH (10 ml) at RT was added $NaBH_4$ (68 mg, 18 mmol) in portions. The reaction was stirred at room temperature for 2 h, then poured into sat.'d $NaHCO_3$. The whole was extracted with CH_2Cl_2 (3x50 ml), the combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated. The crude product (230 mg, 69%) was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (2H, br, Ar<u>H</u>), 7.10 – 7.30 (6H, m, Ar<u>H</u>), 6.30 (1H, s, <u>NH</u>), 4.75 (1H, m, HO<u>CH</u>), 3.60 (2H, t, J = 7.2 Hz, $\underline{CH_2}N$), 2.93 (3H, s, $\underline{CH_3}N$), 2.88 (2H, t, J = 7.6 Hz, $NCH_2\underline{CH_2}$), 2.22 (1H, br, <u>OH</u>), 1.70 (1H, m, HOCHC<u>Ha</u>Hb), 1.50 (1H, m, HOCHCHa<u>Hb</u>), 1.31 (m, 2H, $CH_3\underline{CH_2}$), 0.89 (6H, s, $\underline{(CH_3)_2}C$), 0.80 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$).

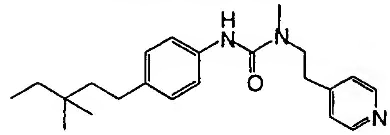
Use of the appropriate starting material and essentially the same procedure afforded the following compounds:



wherein a, R^6, R^7, R^{20} and R^{12} are as defined in the table

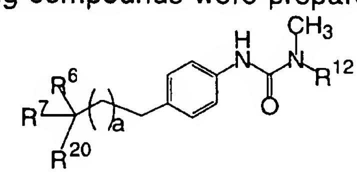
Ex.		a	R^{12}	MS m/e (M+H)
18A		0		370
18B		0		370
18C		0		362
18D		1		362
18E		1		402
18F		0		402
18G		0		376
18H		0		368
18I		0		368
18J		0		360
18K		0		400
18L		0		386

Example 19

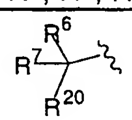
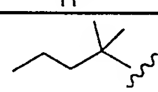
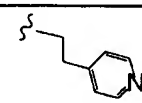
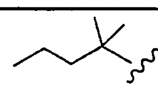
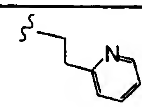
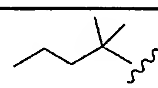
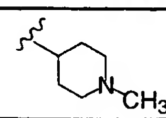
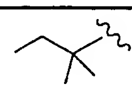
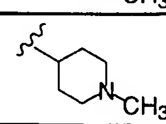
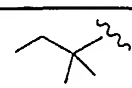
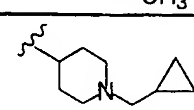


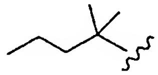
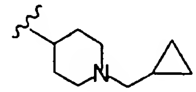
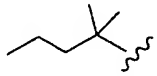
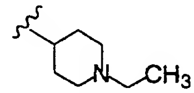
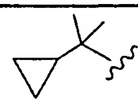
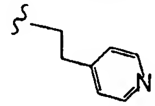
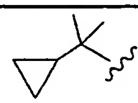
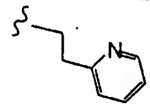
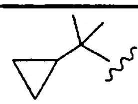
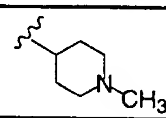
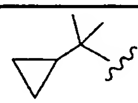
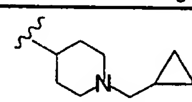
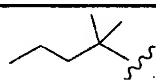
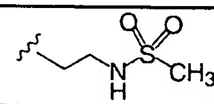
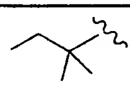
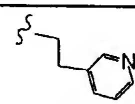
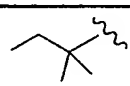
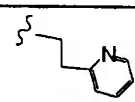
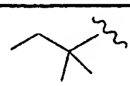
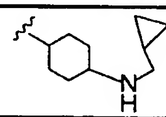
To a solution of Example 18 (230 mg, 0.62 mmol) in dry CH_2Cl_2 (20 ml) was added Et_3SiH (723 mg, 6.2 mmol) and CF_3CO_2H (142 mg, 1.2 mmol). The reaction mixture was stirred at RT for 16 h, then concentrated. The residue was subjected to preparative TLC (1:10 (2M NH_3 in CH_3OH)/CH_2Cl_2) to afford the product (180 mg, 82%) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.50 (2H, m, $\underline{ArH}$), 7.0 – 7.25 (6H, m, $\underline{ArH}$), 6.20 (1H, s, $\underline{NH}$), 3.60 (2H, t, J = 7.2 Hz, $\underline{CH_2}N$), 2.94 (3H, s, $\underline{CH_3}N$), 2.85 (2H, t, J = 7.2 Hz, $\underline{CH_2}CH_2N$), 2.45 (2H, m, $\underline{CH_2}CH_2CMe_2$), 1.40 (2H, m, $CH_2\underline{CH_2}CMe_2$), 1.30 (2H, q, J = 7.2 Hz, $CH_3\underline{CH_2}$), 0.88 (6H, s, $\underline{C(CH_3)_2}$), 0.80 (3H, t, J = 7.6 Hz, $\underline{CH_3}CH_2$). MS (ES) *m/e* 354 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure the following compounds were prepared:

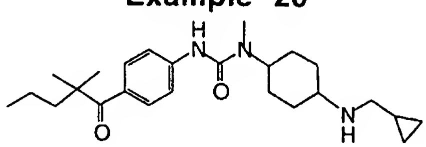


wherein a, R^6, R^7, R^{20} and R^{12} are as defined in the table

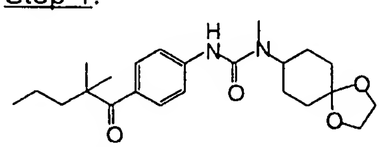
Ex.		a	R^{12}	MS *m/e* (M+H)
19A		0		354
19B		0		354
19C		0		346
19D		1		346
19E		1		386

19F		0		386
19G		0		360
19H		0		352
19I		0		352
19J		0		344
19K		0		384
19L		0		370
19M		1		--
19N		1		--
19O		1		--

Example 20



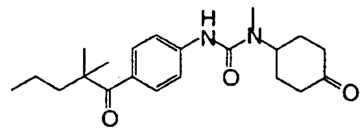
Step 1:



Reaction of Preparation 8 with the product of Example 14, Step 1 according to the procedure of Example 2 afforded the product.

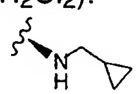
^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (2H, m), 7.42 (2H, m), 6.48 (1H, s), 4.28 (1H, m), 3.95 (4H, s), 2.91 (3H, s), 1.75 (10H, m), 1.30 (6H, s), 1.21 (2H, m), 0.83 (3H, t). MS *m/e* 403 $(M+H)^+$.

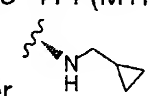
<u>Step 2</u>:



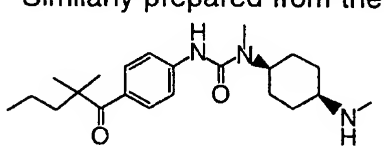
Reaction of the product of Step 1 with HCl by the procedure of Example 14, Step 3, afforded the product. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.77 (2H, m), 7.44 (2H, m), 6.58 (1H, s), 4.81 (1H, m), 2.91 (3H, s), 2.57 (2H, m), 2.46 (2H, m), 2.03 (2H, m), 1.90 (2H, m), 1.75 (2H, m), 1.30 (6H, s), 1.21 (2H, m), 0.83 (3H, t). MS *m/e* 359 $(M+H)^+$.

<u>Step 3</u>: Reaction of the product of Step 2 with cyclopropanemethyl-amine by the procedure of Example 14, Step 4, afforded the product as a mixture of *cis* and *trans* isomers that was separated by preparative tlc (1:9 (2M NH_3 in CH_3OH)/CH_2Cl_2).

20A, less polar*Cis* isomer  : ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (2H, m), 7.44 (2H, m), 6.58 (1H, s), 4.14 (1H, m), 2.94 (3H, s), 2.93 (1H, m), 2.46 (2H, m), 1.85 (4H, m), 1.74 (2H, m), 1.59 (2H, m), 1.46 (2H, m), 1.29 (6H, s), 1.20 (2H, m), 0.98 (1H, m), 0.82 (3H, t, $J = 7.2$ Hz), 0.51 (2H, m), 0.14 (2H, m). MS *m/e* 414 $(M+H)^+$.

20B, more polar *trans* isomer  : ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (2H, m), 7.45 (2H, m), 6.64 (1H, s), 4.16 (1H, m), 2.89 (3H, s), 2.50 (3H, m), 2.05 (2H, m), 1.74 (4H, m,), 1.51 (2H, m), 1.38 (2H, m), 1.29 (6H, s), 1.23 (2H, m), 0.98 (1H, m), 0.82 (3H, t, $J = 7.3$ Hz), 0.49 (2H, m), 0.15 (2H, m). MS *m/e* 414 $(M+H)^+$.

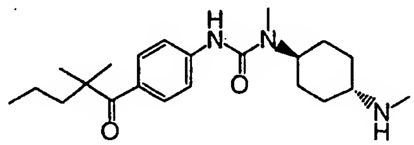
Similarly prepared from the product of Step 2 were:



20C

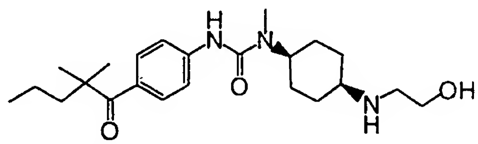
^1H NMR ($CDCl_3$, 400 MHz) δ 7.77 (2H, m), 7.42 (2H, m), 6.50 (1H, s), 4.14 (1H, m), 2.93 (3H, s), 2.72 (1H, m), 2.39 (3H, s), 1.84 (4H, m), 1.76

(2H, m), 1.59 (2H, m), 1.46 (2H, m), 1.30 (6H, s), 1.21 (2H, m), 0.82 (3H, t, $J = 7.2$ Hz). MS *m/e* 374 $(M+H)^+$.



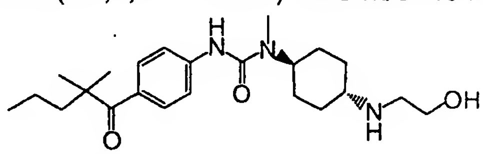
20D

^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (2H, m), 7.42 (2H, m), 6.48 (1H, s), 4.17 (1H, m), 2.89 (3H, s), 2.44 (3H, s), 2.35 (1H, m), 2.05 (2H, m), 1.75 (4H, m), 1.50 (2H, m), 1.46 (2H, m), 1.30 (6H, s), 1.21 (2H, m), 0.83 (3H, t, $J = 7.3$ Hz). MS *m/e* 374 $(M+H)^+$.



20E

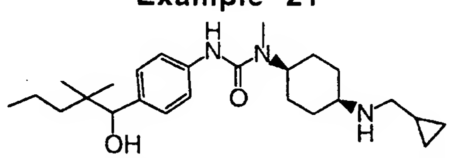
^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (2H, m), 7.43 (2H, m), 6.51 (1H, s), 4.14 (1H, m), 3.70 (2H, m), 2.93 (3H, s), 2.80 (2H, m), 2.52 (1H, m), 1.88 (4H, m), 1.75 (2H, m), 1.71 (2H, m), 1.51 (2H, m), 1.30 (6H, s), 1.21 (2H, m), 0.83 (3H, t, $J = 7.3$ Hz). MS *m/e* 404 $(M+H)^+$.



20F

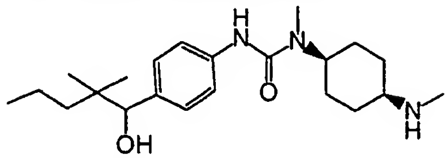
^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (2H, m), 7.43 (2H, m), 6.54 (1H, s), 4.14 (1H, m), 3.70 (2H, m), 2.88 (3H, s), 2.86 (2H, m), 2.51 (3H, m), 2.08 (2H, m), 1.75 (4H, m), 1.51 (2H, m), 1.30 (6H, s), 1.21 (2H, m), 0.83 (3H, t, $J = 7.3$ Hz). MS *m/e* 404 $(M+H)^+$.

Example 21



Reduction of Example 20A with $NaBH_4$ by the procedure of Example 18 afforded the title compound. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34 (2H, m), 7.20 (2H, m), 6.32 (1H, s), 4.40 (1H, s), 4.16 (1H, m), 2.93 (4H, s), 2.46 (2H, m), 1.88 (4H, m), 1.60 (2H, m), 1.49 (2H, m), 1.31 (4H, m), 0.99 (1H, m), 0.87 (6H, s), 0.79 (3H, m), 0.51 (2H, m), 0.15 (2H, m). MS *m/e* 416 $(M+H)^+$.

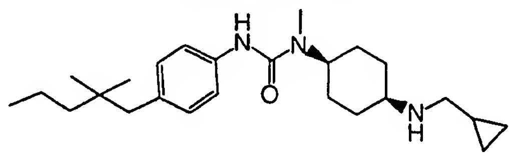
Similarly prepared was:



21A

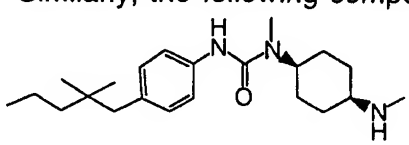
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (2H, m), 7.21 (2H, m), 6.31 (1H, s), 4.41 (1H, s), 4.18 (1H, m), 2.93 (3H, s), 2.78 (1H, m), 2.43 (3H, s), 1.87 (4H, m), 1.62 (2H, m), 1.49 (2H, m), 1.31 (4H, m), 0.87 (6H, s), 0.79 (3H, m). MS *m/e* 376 $(M+H)^+$.

Example 22



Reduction of Example 20 with Et_3SiH/TFA by the procedure of Example 19 afforded the title compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (2H, m), 7.10 (2H, m), 6.26 (1H, s), 4.16 (1H, m), 2.93 (3H, s), 2.89 (1H, m), 2.47 (2H, m), 2.43 (2H, s), 1.87 (4H, m), 1.60 (2H, m), 1.48 (2H, m), 1.31 (2H, m), 1.16 (2H, m), 0.99 (1H, m), 0.88 (3H, t, J = 7.3 Hz), 0.81 (6H, s). 0.50 (2H, m), 0.15 (2H, m). MS *m/e* 400 $(M+H)^+$.

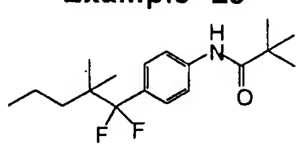
Similarly, the following compound was prepared:



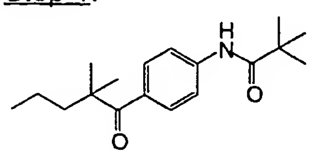
22A

^{1}H NMR (CDC_3, 400 MHz) δ 7.27 (2H, m), 7.01 (2H, m), 6.26 (1H, s), 4.18 (1H, m), 2.92 (3H, s), 2.77 (1H, m), 2.43 (5H, s), 1.88 (4H, m), 1.66 (2H, m), 1.50 (2H, t), 1.30 (2H, m), 1.11 (2H, m), 0.88 (3H, s), 0.81 (6H, s). MS *m/e* 360 $(M+H)^+$.

Example 23



Step 1:

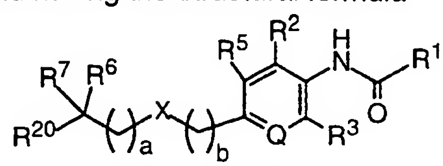


Using the procedure of Example 1, reaction of Preparation 8, trimethyl acetyl chloride and pyridine gave the product. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, J=8.8 Hz, ArH), 7.57 (d, 2H, J=8.4 Hz, ArH), 7.41 (s, 1H, NH), 1.75 (m, 2H, $CH_3CH_2\underline{CH_2}$), 1.32 (s, 9H, $\underline{(CH_3)_3C}$), 1.30 (s, 6H, $\underline{(CH_3)_2C}$), 1.26 (m, 2H, $\underline{CH_2}CH_3$), 0.84 (t, 3H, J = 7.2 Hz, $CH_3\underline{CH_2}$). MS *m/e* 290 $(M+H)^+$.

Step 2: To a solution of the product of Step 1 (100 mg, 0.346 mmol) in dry CH_2Cl_2 (1.0 ml) was added (diethylamino)sulfur trifluoride (557 mg, 3.46 mmol). The reaction mixture was heated at 80 °C overnight, then allowed to cool to RT. The crude mixture was subjected to plc (1:6 EtOAc/hexanes) to give the product (25.0 mg, 23%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 2H, ArH), 7.26 (m, 2H, ArH), 1.32 (m, 13H, $\underline{(CH_3)_3}C$ & $\underline{CH_3CH_2}CH_2$), 0.98 (s, 6H, $\underline{(CH_3)_2}C$), 0.87 (m, 3H, $\underline{CH_3}CH_2$). MS *m/e* 312 $(M+H)^+$.

What is Claimed:

1. A compound having the structural formula

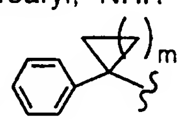


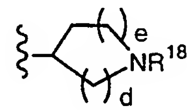
or a pharmaceutically acceptable salt thereof, wherein

a and b are independently 0, 1 or 2, provided that the sum of a and b is 0 to 3;

Q is $=\underset{\underset{R^4}{|}}{C}-$ or $-N=$;

X is -O-, -S-, -SO-, $-SO_2-$, $-CH(OR^8)-$, -C(O)-, $-C(R^{23})_2-$, $-C(R^{25})=C(R^{25})-$, $-C\equiv C-$ or $-\overset{\overset{NOR^8}{\|}}{C}-$;

R^1 is R^{15}-aryl, R^{24}-heteroaryl, $-NHR^{12}$, $-N(R^{12})_2$, $-(C_1-C_9)$alkyl-$OC(O)R^8$, aryloxy(C_1-C_9)alkyl,  wherein m is 1-4, or

 wherein d and e are independently 0, 1 or 2;

R^2, R^3, R^4 and R^5 are independently selected from the group consisting of H, C_1-C_5 straight or branched alkyl, (C_3-C_{12})cycloalkyl, R^{14}-(C_3-C_{12})cycloalkyl, halogen, $-OR^8$, $-N(R^8)_2$, $-CO_2R^8$ and CF_3;

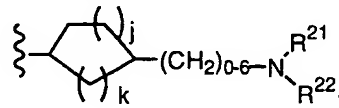
R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_9)alkyl, (C_1-C_9)alkenyl, hydroxy-(C_1-C_9)alkyl, amino-(C_1-C_9)-alkyl, (C_1-C_9)alkoxy-(C_1-C_9)alkyl, (C_3-C_{12})cycloalkyl and (C_3-C_{12})-cycloalkyl-(C_1-C_6)alkyl, or R^6 and R^7, together with the carbon to which they are attached, form a 3, 4, 5, 6 or 7-membered carbocyclic ring, or a 4, 5, 6 or 7-membered heterocyclic ring, wherein 1, 2 or 3 ring members are independently selected from the group consisting of O, S and N;

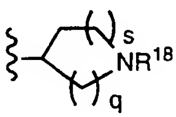
R^8 is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, R^{15}-aryl and R^{24}-heteroaryl;

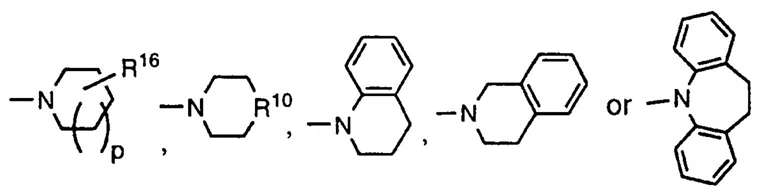
R^9 is (C_1-C_6)alkyl, (C_3-C_{12})cycloalkyl, R^{15}-aryl or R^{24}-heteroaryl;

R^{11} is independently selected from the group consisting of H, (C_1-C_6)alkyl and (C_3-C_{12})cycloalkyl;

R^{12} is independently selected from the group consisting of straight or branched $(C_1\text{-}C_9)$alkyl, hydroxy$(C_2\text{-}C_9)$alkyl, $(C_1\text{-}C_9)$alkoxy-$(C_2\text{-}C_9)$-alkyl, $N(R^{11})(R^{19})$-$(C_2\text{-}C_9)$-alkyl, HS$(C_2\text{-}C_9)$-alkyl, $(C_1\text{-}C_9)$-alkylthio-$(C_2\text{-}C_9)$-alkyl, $(C_3\text{-}C_{12})$-cycloalkyl, R^{14}-$(C_3\text{-}C_{12})$ cycloalkyl, R^{15}-aryl,
R^{24}-heteroaryl, R^{15}-aryl$(C_1\text{-}C_6)$-alkyl, R^{24}-heteroaryl$(C_1\text{-}C_6)$-alkyl,


wherein j and k are independently 0, 1 or 2,


and wherein q is 1 or 2, and s is 0, 1 or 2; or two R^{12} groups, together with the nitrogen to which they are attached, form a ring of the formula



wherein p is 0, 1 or 2;

R^{10} is $-NR^{18}-$, -O- or -S-;

R^{13} is 1 to 3 substituents independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, halogen, $(C_1\text{-}C_6)$alkoxy and CF_3;

R^{14} is 1 to 3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, benzyl, R^{13}-aryl and R^{13}-heteroaryl;

R^{15} is 1 to 3 substituents independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, halo, polyhalo$(C_1\text{-}C_6)$alkyl, $R^{17}O$-, $-N(R^{17})_2$, $-S(R^{17})$, $R^{17}O$-$(C_1\text{-}C_6)$alkyl, $(R^{17})_2N$-$(C_1\text{-}C_6)$alkyl, formyl, $-C(O)R^{17}$, $-COOR^{17}$, $-CON(R^{17})_2$, $-OC(O)N(R^{17})_2$, $-N(R^{17})C(O)N(R^{17})_2$, $-NR^{17}C(O)R^{17}$, $-NR^{17}C(O)OR^{14}$, $R^{17}S(O)$-, $R^{17}SO_2$-, $R^{17}SO_2NR^{17}$- and tri$(C_1\text{-}C_6)$-alkylsilyl;

R^{16} is 1-3 substituents independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{12})$spirocyclo-alkyl, $(C_3\text{-}C_4)$spiro-alkylenedioxy, R^{15}-aryl, R^{24}-heteroaryl, benzyl, N-piperidinyl, $-COR^8$, $-C(O)NR^8R^9$, $-NR^8R^9$ and $-NR^8C(O)R^9$, or when two

R^{16} groups are attached to adjacent ring carbon atoms, together with said carbon atoms, they can form a $(C_5\text{-}C_7)$cycloalkyl ring;

R^{17} is independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{12})$cycloalkyl$(C_1\text{-}C_6)$alkyl, R^{13}-aryl and R^{13}-heteroaryl;

R^{18} is independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{12})$cycloalkyl-$(C_1\text{-}C_6)$alkyl, R^{15}-aryl, R^{24}-heteroaryl, $-CO_2R^9$, $-C(O)N(R^8)_2$, $-COR^8$ and $-SO_2R^9$;

R^{19} is H, $(C_3\text{-}C_{12})$cycloalkyl-$(C_1\text{-}C_6)$alkyl, R^{15}-aryl, R^{24}-heteroaryl, $-CO_2R^9$, $-C(O)N(R^8)_2$, $-COR^8$ or $-SO_2R^9$;

R^{20} is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{12})$cycloalkyl-$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, oxo$(C_1\text{-}C_6)$alkyl or polyhalo$(C_1\text{-}C_6)$alkyl;

R^{21} and R^{22} are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl-$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, R^{15}-aryl, R^{24}-heteroaryl, R^{15}-aryl$(C_1\text{-}C_6)$alkyl or R^{24}-heteroaryl$(C_1\text{-}C_6)$-alkyl;

R^{23} is independently selected from the group consisting of H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, R^{15}-aryl, and R^{24}-heteroaryl;

R^{24} is 1 to 2 substituents independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, halo, polyhalo$(C_1\text{-}C_6)$alkyl, $R^{17}O$-, $-N(R^{17})_2$, $-S(R^{17})$, $R^{17}O$-$(C_1\text{-}C_6)$alkyl, $(R^{17})_2N$-$(C_1\text{-}C_6)$alkyl, formyl, $-C(O)R^{17}$, $-COOR^{17}$, $-CON(R^{17})_2$, $-OC(O)N(R^{17})_2$, $-N(R^{17})C(O)N(R^{17})_2$, $-NR^{17}C(O)R^{17}$, $-NR^{17}C(O)OR^{14}$, $R^{17}S(O)$-, $R^{17}SO_2$-, $R^{17}SO_2NR^{17}$- and tri$(C_1\text{-}C_6)$-alkylsilyl; and

R^{25} is independently selected from the group consisting of hydrogen, halogen, $(C_1\text{-}C_6)$-alkyl and polyhalo$(C_1\text{-}C_6)$alkyl.

2. A compound of claim 1 wherein Q is $=\underset{R^4}{\underset{|}{C}}-$.

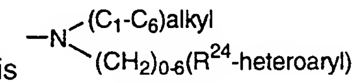
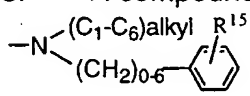
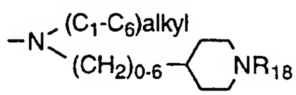
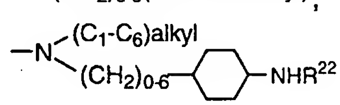
3. A compound of claim 1 wherein R^3 and R^4 are each H; and R^2 and R^5 are independently selected from the group consisting of hydrogen and halogen.

4. A compound of claim 1 wherein X is -S-; -C(O)-; $-CH(OR^8)$- or $-C(R^{23})_2$-.

5. A compound of claim 4 wherein X is $-C(R^{23})_2-$ and R^{23} is hydrogen.

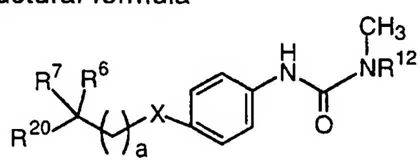
6. A compound of claim 1 wherein a is 1 or 2 and b is 0.

7. A compound of claim 1 wherein R^1 is $-NHR^{12}$ or $-N(R^{12})_2$.

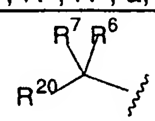
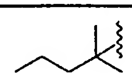
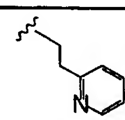
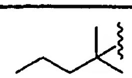
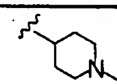
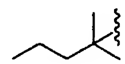
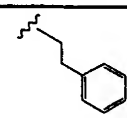
8. A compound of claim 7 wherein R^1 is ; ; ; or , wherein R^{18} is $(C_1\text{-}C_6)$alkyl or $-SO_2R^9$; R^9 is $(C_1\text{-}C_6)$alkyl or aryl; and R^{22} is $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_{12})$cycloalkyl$(C_1\text{-}C_6)$alkyl.

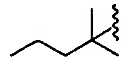
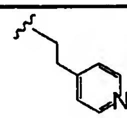
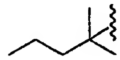
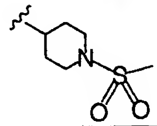
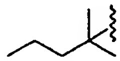
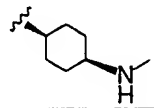
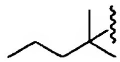
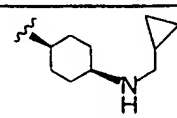
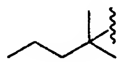
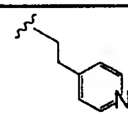
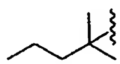
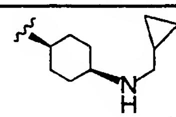
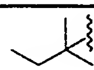
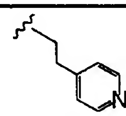
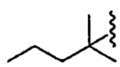
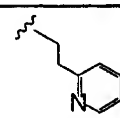
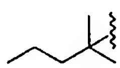
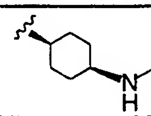
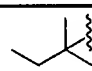
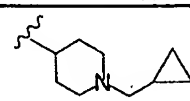
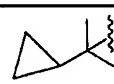
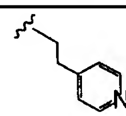
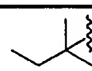
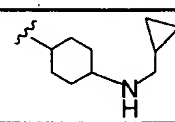
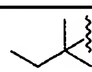
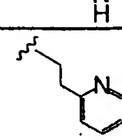
9. A compound of claim 1 wherein R^6 and R^7 are each $(C_1\text{-}C_6)$alkyl, or R^6 and R^7, together with the carbon to which they are attached, form a $C_3\text{-}C_6$ carbocyclic ring.

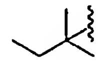
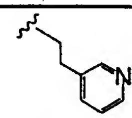
10. A compound of claim 1 selected from the group consisting of those having the structural formula



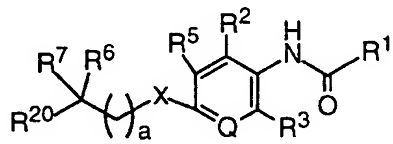
wherein R^{20}, R^6, R^7, a, X, and R^{12} are as defined in the following table:

	a	X	R^{12}
	0	S	
	0	S	
	0	S	

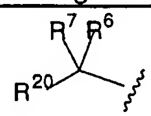
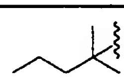
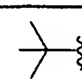
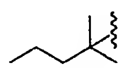
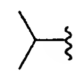
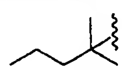
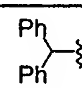
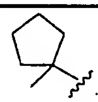
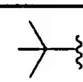
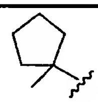
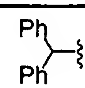
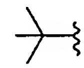
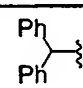
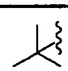
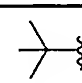
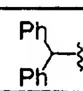
	0	S	
	0	S	
	0	S	
	0	S	
	0	CH_2	
	0	CH_2	
	1	CH_2	
	0	CH_2	
	0	CH_2	
	1	CH_2	
	0	CH_2	
	1	CH_2	
	1	CH_2	

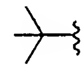
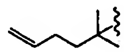
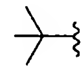
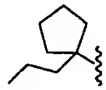
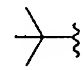
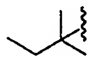
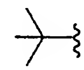
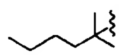
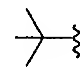
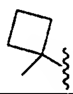
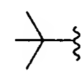
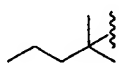
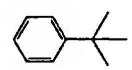
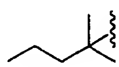
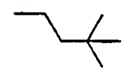
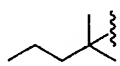
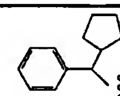
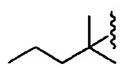
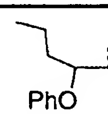
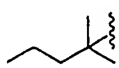
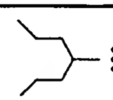
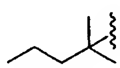
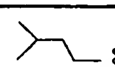
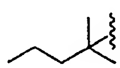
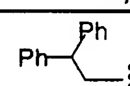
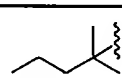
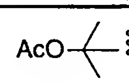
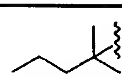
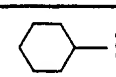
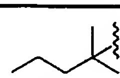
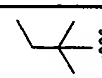
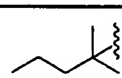
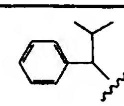
	1	CH_2	

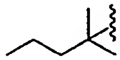
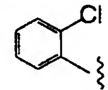
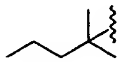
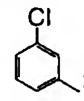
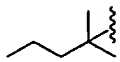
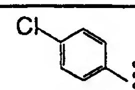
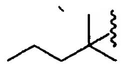
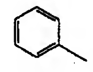
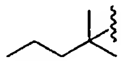
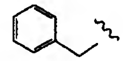
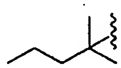
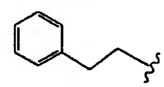
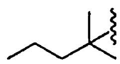
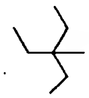
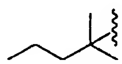
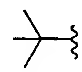
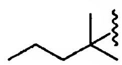
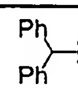
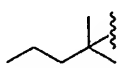
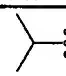
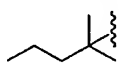
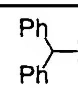
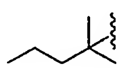
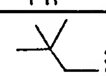
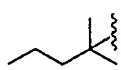
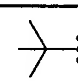
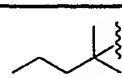
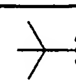
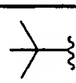
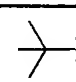
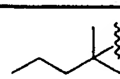
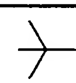
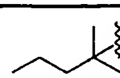
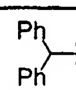
11. A compound selected from the group consisting of those having the structural formula

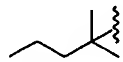
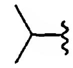
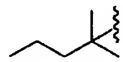
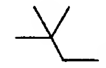
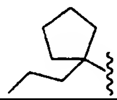
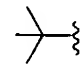
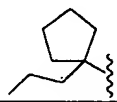
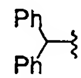
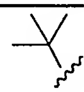
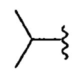
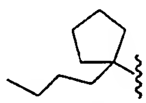
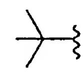
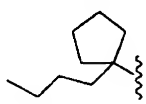
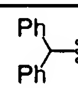
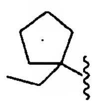
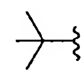
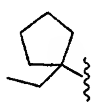
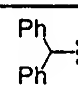
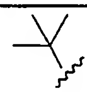
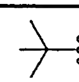
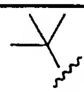
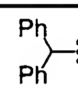
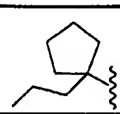
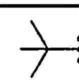
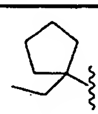
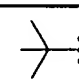
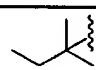
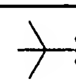
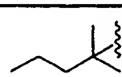
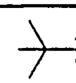


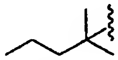
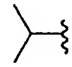
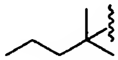
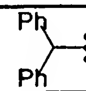
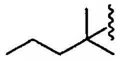
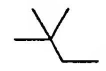
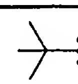
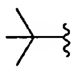
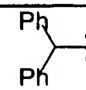
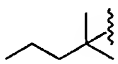
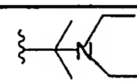
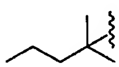
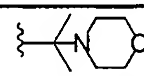
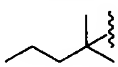
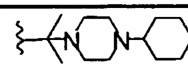
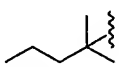
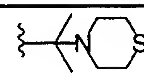
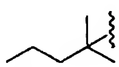
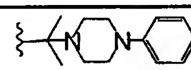
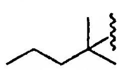
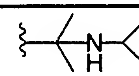
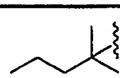
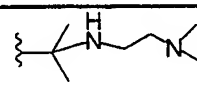
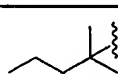
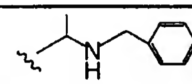
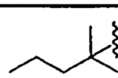
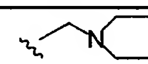
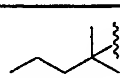
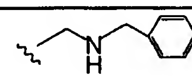
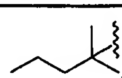
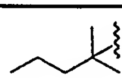
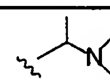
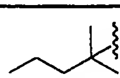
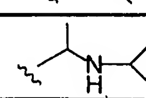
wherein R^{20}, R^6, R^7, a, X, R^5, R^2, R^3, Q and R^1 are as defined in the following table:

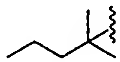
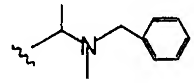
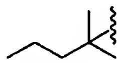
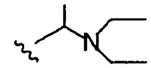
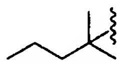
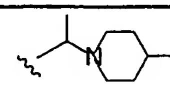
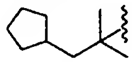
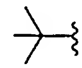
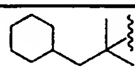
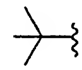
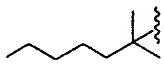
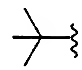
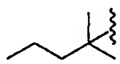
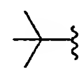
	a	X	Q	R^2	R^3	R^5	R^1
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	

	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	

	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	F	
	0	S	C	H	H	F	
	0	S	C	H	H	Cl	
	0	S	C	H	H	Cl	
	0	S	C	H	H	Cl	
	0	S	C	H	H	Cl	
	0	S	C	F	H	H	
	1	S	C	H	H	H	
	0	O	C	H	H	H	
	0	O	C	H	H	H	

	0	O	C	H	H	H	
	0	O	C	H	H	H	
	0	O	C	H	H	H	
	0	O	C	H	H	H	
	1	O	C	H	H	H	
	0	O	C	H	H	H	
	0	O	C	H	H	H	
	0	O	C	H	H	H	
	0	O	C	H	H	H	
	1	O	C	H	H	H	
	1	O	C	H	H	H	
	1	O	C	H	H	H	
	1	O	C	H	H	H	
	1	O	C	H	H	H	
	1	O	C	H	H	H	

	0	O		H	H	H	
	0	O		H	H	H	
	0	O		H	H	H	
	0	S	N	H	H	H	
	0	S	N	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	

	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	S	C	H	H	H	
	0	$-CF_2-$	C	H	H	H	

12. A pharmaceutical composition comprising a compound as defined in claim 1 in combination with a pharmaceutically acceptable carrier.

13. The use of a compound of claim 1 for the preparation of a medicament for treating an eating disorder or diabetes.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 99/11795

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C321/02 C07C311/00 C07D211/96 A61K31/10 A61K31/18
A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 20821 A (CIBA GEIGY AG ;RUEEGER HEINRICH (CH); SCHMIDLIN TIBUR (CH); RIGOLL) 12 June 1997 (1997-06-12) the whole document ---	1
P,A	WO 98 35957 A (BAYER AG) 20 August 1998 (1998-08-20) cited in the application the whole document -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 1999	12/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goetz, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

..formation on patent family members

Inter' onal Application No

PC1/US 99/11795

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WO 9720821	A	12-06-1997	AU	7692696 A	27-06-1997
WO 9835957	A	20-08-1998	AU	6144098 A	08-09-1998
			CA	2251368 A	20-08-1998
			EP	0910565 A	28-04-1999